CLINICAL STUDY PROTOCOL

Protocol Title:

A Phase I/II study to investigate the safety and immunogenicity of Quadrivalent Influenza mRNA Vaccines MRT5421, MRT5424, and MRT5429 in healthy participants aged 18 years and above

Study Code: VAV00045

Amendment Number: not applicable

Compound: Quadrivalent Influenza mRNA vaccine

Brief Title:

A study to investigate the safety and immunogenicity of the quadrivalent influenza mRNA vaccines in adults aged 18 years and above

Study Phase: I/II

Sponsor Name and Legal Registered Address:

Sanofi Pasteur Inc.
Discovery Drive, Swiftwater, PA 18370-0187, USA

Manufacturer: Same as Sponsor

Regulatory Agency Identifier Numbers:

Registry	ID
WHO UTN	U1111-1295-2852
IND	030196

Protocol Version Number: 3.0

Approval Date: 12 March 2024

Medical Monitors Name and Function:

Responsible medical officer (RMO): [redacted]., Global Clinical Development Strategy Expert-Vaccines

The study centers, the investigators at each center, and the coordinating investigator(s) (if applicable) are listed in a separate document.

DOCUMENT HISTORY

Previous Version	Date	Comments
1.0	11 December 2023	Version submitted to IRB (US & Puerto Rico)
2.0	11 January 2024	Version submitted to IRB & CBER. Updates of this version of protocol following CBER request.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

Ab:	antibody
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
AR:	adverse reaction
AST:	aspartate aminotransferase
CAC:	Cardiac adjudication Committee
CI:	confidence interval
CRF:	case report form
CRP:	C-reactive protein
D:	day
DNA:	deoxyribonucleic acid
ECG:	electrocardiogram
ELISA:	enzyme-linked immunosorbent assay
ESDR:	early safety data review
FSH:	follicle stimulating hormone
GBS:	Guillain-Barré syndrome
GCP:	Good Clinical Practice
GDPR:	General Data Protection Regulation
GMT:	geometric mean titer
GMTR:	geometric mean titer ratio
GPV:	Global Pharmacovigilance
HA:	hemagglutinin
HAI:	hemagglutinin inhibition
HRT:	hormonal replacement therapy
IB:	Investigator's Brochure
ICF:	informed consent form
ICH:	International Council for Harmonisation
IEC:	Independent Ethics Committees
[redacted]	
IRB:	Institutional Review Boards
IRT:	Interactive Response Technology
LLOQ:	lower limit of quantitation
LNP:	Lipid nanoparticle
MAAE:	medically attended adverse event
MDCK:	Madin-Darby canine kidney
medDRA:	Medical Dictionary for Regulatory Activities
mFAS:	modified full analysis set
mRNA:	messenger ribonucleic acid
QIV mRNA:	quadrivalent modified mRNA influenza vaccine
QIV-HD:	high-dose quadrivalent influenza vaccine

QIV-SD:	standard dose quadrivalent influenza vaccine
RBC:	red blood cell
RCDC:	reverse cumulative distribution curve
RMO:	Responsible medical officer
SAE:	serious adverse event
SAP:	statistical analysis plan
SMT:	Safety Management Team
SoA:	Schedule of Activities
SP:	Sanofi Pasteur
WBC:	white blood count
WHO:	World Health Organization

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol Title:

A Phase I/II study to investigate the safety and immunogenicity of Quadrivalent Influenza mRNA Vaccines MRT5421, MRT5424, and MRT5429 in healthy participants aged 18 years and above

Brief Title:

A study to investigate the safety and immunogenicity of the quadrivalent influenza mRNA vaccines in adults aged 18 years and above

Regulatory Agency Identifier Numbers:

Registry	ID
WHO UTN	U1111-1295-2852
IND	030196

Rationale:

The objective of study VAV00045 is to evaluate the safety and immunogenicity of different formulations of quadrivalent influenza modified messenger ribonucleic acid vaccines (QIV mRNA), MRT5421, MRT5424, and MRT5429, administered as a single [redacted] in adult 18 years of age and older, compared to each other and to the 3 following active controls: standard-dose Fluzone® quadrivalent influenza vaccine (QIV-SD, Sanofi Pasteur [SP]); Fluzone high-dose quadrivalent influenza vaccine (QIV-HD, SP), which will be a comparator for study participants ≥ 65 years of age only; or quadrivalent recombinant influenza vaccine (RIV4, SP).

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Safety objective • To describe the safety profile of each QIV mRNA compared to each other and to QIV-SD, RIV4, or QIV-HD* in all participants and in each age group	***Safety endpoints*** • Presence of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after injection • Presence of solicited injection site reactions (ie, pre-listed in the participant diary and in the case report form [CRF]) occurring up to 7 days after injection • Presence of solicited systemic reactions (ie, pre-listed in the participant diary and in the CRF) occurring up to 7 days after injection

	• Presence of unsolicited AEs reported up to 28 days after injection • Presence of medically attended adverse events (MAAEs) reported up to 180 days after injection • Presence of serious adverse event (SAEs) and adverse events of special interest (AESIs) throughout the study • Presence of out-of-range biological test results (including shift from baseline values) up to 8 days after injection†

Immunogenicity objective
• To describe the HAI immune response induced by each QIV mRNA compared to each other and to QIV-SD, RIV4, or QIV-HD* in all participants and in each age group
	Immunogenicity endpoints
	• Hemagglutinin inhibition (HAI) antibody (Ab) response to each homologous strain at Day (D)29:
	  • HAI titers at D01 and D29
	  • Detectable HAI titer (HAI titer ≥ 10 [1/dil]) at D01 and D29
	  • Individual HAI Ab titer ratio D29/D01
	  • Seroconversion (HAI Ab titer < 10 [1/dil] at D01 and post-injection titer ≥ 40 [1/dil] at D29, or titer ≥ 10 [1/dil] at D01 and a ≥ 4-fold increase in titer [1/dil] at D29)
	  • HAI Ab titer ≥ 40 (1/dil) at D29
	  • 2-fold and 4-fold rise in HAI titers from D01 to D29

Secondary	

• To describe the neutralizing Ab immune response induced by each QIV mRNA compared to each other and to QIV-SD, RIV4, or QIV-HD* in all participants and in each age group	• Neutralizing Ab response to each homologous strain at D29
	  • Neutralizing Ab titers at D01 and D29
	  • Individual neutralizing antibodies titer ratio D29/D01
	  • 2-fold and 4-fold increase in neutralizing titers from D01 to D29

* QIV-HD will only be administered to adults ≥ 65 years of age

† Safety laboratory assessments will include serum chemistries (liver enzymes including aspartate aminotransferase [AST], alanine aminotransferase [ALT], total and direct bilirubin, C-reactive protein [CRP], creatinine); hematology (white blood count [WBC] with differential, hemoglobin, platelet count, and red blood cell [RBC] count); and troponin I (for screening for potential myocarditis cases, systematically tested at D01 and D03, and at D09 only in case of abnormal values in previous samples).

Overall Design:

Type of design	Parallel, with dose-escalation for sentinel cohort, multi-center
Phase	I / II
Control method	Active-controlled (control = QIV-SD, QIV-HD [adults ≥ 65 years of age only], RIV4)
Study population	Adults 18 years of age and older
Countries	US, Puerto Rico, Honduras
Level and method of blinding	Modified double-blind (sentinel and main cohorts) (Participants; Sites except for those preparing/administering study intervention; Sponsor except Sponsor's unblinded internal safety review committee)
Investigational intervention assignment method	Randomization

Inclusion/Exclusion Criteria

Inclusion criteria

Participants are eligible for the study only if all of the following criteria are met:

Age

I 01. Aged from 18 years on the day of inclusion[a] or aged from 21 years on the days of inclusion[b], depending on the countries.

Sex, contraceptive/barrier method and pregnancy testing requirements

I 02. A female participant is eligible to participate if she is not pregnant or breastfeeding and one of the following conditions applies:

- Is of non-childbearing potential. To be considered of non-childbearing potential, a female must be postmenopausal for at least 1 year, or surgically sterile.

  OR

- Is of childbearing potential and agrees to use an effective contraceptive method or abstinence from at least 4 weeks prior to study intervention administration until at least 12 weeks after study intervention administration.

A female participant of childbearing potential must have a negative highly sensitive pregnancy test (urine or serum as required by local regulation) within 8 hours before the 1st dose of study intervention.

[a] "18 years" means from the day of the 18th birthday, for participants in US
[b] "21 years" means from the day of the 21st birthday for participants in Puerto Rico and Honduras

Informed Consent

I 03. Informed consent form has been signed

Other Inclusions

I 04. Able to attend all scheduled visits and to comply with all study procedures

Exclusion criteria

Participants are not eligible for the study if any of the following criteria are met:

Medical conditions

E 01. Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)

E 02. Known systemic hypersensitivity to any of the study intervention components (eg, polyethylene glycol, polysorbate); history of a life-threatening reaction to the study interventions used in the study or to a product containing any of the same substances; any allergic reaction (eg, anaphylaxis) after administration of mRNA vaccine

E 03. Previous history of myocarditis, pericarditis, and / or myopericarditis

E 04. Known history of previous episodes of Gillian-Barre Syndrome (GBS), neuritis (including Bell's palsy), convulsions, encephalitis, transverse myelitis, and vasculitis

E 05. Participants with an electrocardiogram (ECG) that is consistent with possible myocarditis or pericarditis or, in the opinion of the investigator, demonstrates clinically relevant abnormalities that may affect participant safety or study results

E 06. Self-reported thrombocytopenia, contraindicating IM injection based on investigator's judgment

E 07. Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating IM injection based on investigator's judgment

E 08. Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with study conduct or completion[a]

[a] Chronic illness may include, but is not limited to, cardiac disorders, renal disorders, auto-immune disorders, diabetes, psychiatric disorders, or chronic infection

E 09. Moderate or severe acute illness / infection (according to investigator's judgment) or febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]) on the day of study intervention administration. A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided

E 10. Alcohol, prescription drug, or substance abuse that, in the opinion of the investigator, might interfere with the study conduct or completion

E 11. Participant who had acute infection symptoms or a positive SARS-CoV-2 RT-PCR or antigen test in the past 10 days prior to the first visit (V01)

Prior/concomitant therapy

E 12. Receipt of any vaccine in the 4 weeks preceding study intervention administration or planned receipt of any vaccine in the 4 weeks following study intervention administration[a]

E 13. Receipt of immune globulins, blood or blood-derived products in the past 3 months

E 14. Previous vaccination against influenza in the previous 6 months with an investigational or marketed vaccine

E 15. Receipt of any mRNA vaccine/product in the 2 months preceding study intervention administration

Prior/concurrent clinical study experience

E 16. Participation at the time of study enrollment (or in the 4 weeks preceding the study intervention administration) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure

Other exclusions

E 17. Self-reported or documented seropositivity for human immunodeficiency virus, hepatitis B virus, or hepatitis C virus

E 18. Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily

E 19. Any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives, including planning to leave the area of the study before the end of the study or participation in strenuous or endurance exercise through V03

[a] If the participant is enrolled and seeks vaccination of an authorized influenza vaccine or COVID-19 vaccine outside of the study, he / she will be encouraged to discuss this intention proactively with the study investigator and will be permitted to receive the authorized vaccine at the earliest 28 days after study vaccination and at any time thereafter. If the participant receives the authorized influenza vaccine or COVID-19 vaccine, this information will be collected. Participants will continue to be followed up for the duration of the study as per scheduled visits and procedures

E 20. Identified as an investigator or employee of the investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (ie, parent, spouse, natural or adopted child) of the investigator or employee with direct involvement in the proposed study

If the participant has a primary physician who is not the investigator, the site may contact this physician with the participant's consent to inform him / her of the participant's participation in the study. In addition, the site should ask this primary physician to verify exclusion criteria relating to previous therapies, such as receipt of blood products or previous vaccines.

Brief Summary:

The purpose of this study is to evaluate the safety and immunogenicity of a single [redacted] of different formulations of QIV mRNA (MRT5421, MRT5424, and MRT5429) compared to an active control (QIV-SD, QIV-HD [adults ≥ 65 years of age only], or RIV4) in adults 18 years of age and older. The enrollment of participants will be performed in a stepwise manner, based on early safety data reviews (ESDRs) performed by an internal Sponsor Safety Management Team (SMT). Further details on the enrollment strategy and ESDRs are presented in Figure 2.

Participants who did not receive a licensed seasonal influenza vaccine during the study conduct will be included into the Ab persistence up to D181 and will be followed up for safety up to D366. Participants who did receive a licensed seasonal influenza vaccine during the study conduct will only be followed up for safety up to D366.

Study details include:

- Study duration per participant: approximately 12 months
- Treatment duration: 1 injection of one of the 7 QIV mRNA or one of the controls
- Dose escalation with sequential enrollment (sentinel cohort followed by main cohort)

Number of Participants:

A total of up to 1002 participants is planned to be randomized, with 266 participants in the sentinel safety cohorts and 736 participants in the main cohort. The study will target recruitment of racial and ethnic diversity that will be representative of the countries in which the study will be conducted.

The planned number of participants in the sentinel safety cohorts and in the main cohort are presented in Table 1 and Table 2.

Table 1: Sentinel safety cohorts - Planned sample size

Cohort	Group	Group Name	Total quantity of mRNA (µg) per dose	Number of participants (n) (N = 266)		Total number of participants
				18-64 years	≥ 65 years	
Sentinel safety cohort 1	1	QIV mRNA / [redacted] (MRT5421)	192	-	-	147
	2	QIV mRNA [redacted] MRT5429)	30	14	14	
	3	QIV mRNA [redacted] MRT5429)	96	14	14	
	4	QIV mRNA / [redacted] (MRT5429)	132	14	14	
	5	QIV mRNA / [redacted] (MRT5429)	192	-	-	
	6	QIV mRNA / [redacted] (MRT5424)	96	14	14	
	7	QIV mRNA / [redacted] (MRT5424)	192	-	-	
	8	QIV-SD	-	7	7	
	9	QIV-HD	-	-	7	
	10	RIV4	-	7	7	
Sentinel safety cohort 2	1	QIV mRNA / [redacted] (MRT5421)	192	14	14	119
	2	QIV mRNA / [redacted] (MRT5429)	30	-	-	
	3	QIV mRNA / [redacted] (MRT5429)	96	-	-	
	4	QIV mRNA / [redacted] (MRT5429)	132	-	-	
	5	QIV mRNA / [redacted] (MRT5429)	192	14	14	
	6	QIV mRNA / [redacted] (MRT5424)	96	-	-	
	7	QIV mRNA / [redacted] (MRT5424)	192	14	14	
	8	QIV-SD	-	7	7	
	9	QIV-HD	-	-	7	
	10	RIV4	-	7	7	
Total number of participants:				**126**	**140**	

[redacted]

Table 2: Main cohort - Planned sample size

Cohort	Group	Group Name	Total quantity of mRNA (µg) per dose	Number of participants (n) (N = 736)	
				18-64 years	≥ 65 years
Main	1	QIV mRNA / [redacted] MRT5421)	192	23	23
	2	QIV mRNA [redacted] MRT5429)	30	-	-
	3	QIV mRNA [redacted] MRT5429)	96	46	46
	4	QIV mRNA / [redacted] MRT5429)	132	46	46
	5	QIV mRNA / [redacted] MRT5429)	192	46	46
	6	QIV mRNA / [redacted] (MRT5424)	96	46	46
	7	QIV mRNA / [redacted] (MRT5424)	192	46	46
	8	QIV-SD	-	46	46
	9	QIV-HD	-	-	46
	10	RIV4	-	46	46
Total number of participants:				**345**	**391**

[redacted]

Study Arms and Duration:

In each age group (18 to 64 years age group and 65 years and older age group), eligible participants will be randomized to receive a single IM injection of either MRT5421, MRT5424, MRT5429, QIV-SD, RIV4, or QIV-HD[a] at Day (D)01.

The duration of each participant's participation will be approximately 12 months.

Study Interventions:

[a] QIV-HD will only be administered to adults ≥ 65 years of age

Table 3: Identity of experimental study interventions

Group Number	1	2	3	4	5	6	7
Group Name	QIV mRNA [redacted] (MRT5421)	QIV mRNA [redacted] (MRT5429)	QIV mRNA [redacted] (MRT5429)	QIV mRNA [redacted] (MRT5429)	QIV mRNA [redacted] (MRT5429)	QIV mRNA [redacted] (MRT5424)	QIV mRNA [redacted] (MRT5424)
Intervention Name	QIV mRNA [redacted] NH22/23	QIV mRNA [redacted] NH22/23				QIV mRNA [redacted] NH22/23	
Use	Experimental	Experimental	Experimental	Experimental	Experimental	Experimental	Experimental
IMP or NIMP/AxMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP
Type	Vaccine	Vaccine	Vaccine	Vaccine	Vaccine	Vaccine	Vaccine
Presentation		Suspension for injection in a vial					
Formulation / Dosage	[redacted] QIV mRNA MRT5421 per dose (LNP [redacted]): quantities of full-length of HA mRNA from each strain of 2022- [redacted]	[redacted] QIV mRNA MRT5429 per dose (LNP [redacted]): quantities of full-length of HA mRNA from each strain of 2022- [redacted]	[redacted] QIV mRNA MRT5429 per dose (LNP [redacted]): quantities of full-length of HA mRNA from each strain of 2022- [redacted]	[redacted] QIV mRNA MRT5429 per dose (LNP [redacted]): quantities of full-length of HA mRNA from each strain of 2022-2023 NH strains: [redacted]	[redacted] QIV mRNA MRT5429 per dose (LNP [redacted]): quantities of full-length of HA mRNA from each strain of 2022-2023 NH strains: [redacted]	[redacted] QIV mRNA MRT5424 per dose (LNP [redacted]): quantities of full-length of HA mRNA from each strain of 2022-2023 NH strains: [redacted]	[redacted] QIV mRNA MRT54254 per dose (LNP [redacted]): quantities of full-length of HA mRNA from each strain of 2022-2023 NH strains: [redacted]

Excipient / Diluent	[redacted]						
IMP preparation							
Dosage Level							
Number of Doses / Dosing Interval							
Route of Administration							
Site of Administration							
Sourcing	Provided by the Sponsor	Provided by the Sponsor	Provided by the Sponsor	Provided by the Sponsor	Provided by the Sponsor	Provided by the Sponsor	Provided by the Sponsor
Packaging and Labeling	Each vial will be labeled and packed in separate boxes (mRNA and diluents) due to the temperature differences. Each vial and each box will bear fixed label containing the dose number. All will be labeled as required per country requirement.						
Storage Conditions	[redacted]						

AxMP, auxiliary medicinal product; [redacted] IMP, investigational medicinal product; NH, Northern hemisphere; NIMP, non-investigational medicinal product; PBS, phosphate-buffered saline

Table 4: Identity of control study interventions

Group Number	8	9	10
Intervention Name	QIV-SD (Fluzone Quadrivalent vaccine) NH22/23	QIV-HD (Fluzone high-dose quadrivalent influenza vaccine) NH22/23	RIV4 (Flublok Quadrivalent vaccine) NH22/23
Use	Active control	Active control	Active control
IMP or NIMP/AxMP	IMP	IMP	IMP
Type	Vaccine	Vaccine	Vaccine
Dose Form	Suspension for injection in pre-filled syringe	Suspension for injection in pre-filled syringe	Solution for injection in pre-filled syringe
Formulation / Dosage	[redacted] HA per dose: [redacted] of HA per strain from 2022-2023 NH strains	[redacted] HA per dose: [redacted] of HA per strain from 2022-2023 NH strains	[redacted] HA per dose: [redacted] of HA per strain from 2022-2023 NH strains
Dosage Level	[redacted]		
Number of Doses / Dosing Interval			
Route of Administration			
Site of Administration			
Sourcing	Provided by the Sponsor	Provided by the Sponsor	Provided by the Sponsor
Packaging and Labeling	Each study intervention will be provided in a pre-filled syringe for direct injection. Each syringe and each box will bear fixed label containing the dose number. All will be labeled as required as per country requirement.		
Storage Conditions	[redacted]		

AxMP, auxiliary medicinal product; [redacted] IMP, investigational medicinal product; NH, Northern hemisphere; NIMP, non-investigational medicinal product

Statistical Considerations:

No statistical hypotheses will be tested. Statistics will be descriptive. The modified Full Analysis Set (mFAS) population will be used for the immunogenicity analyses and the safety. The mFAS is defined as participant injected and analyzed according to the group/product received.

Primary safety endpoints

Safety endpoints will be described according to the vaccine received and by age group (18-64 years and ≥ 65 years of age). The main parameters will be described using 95% confidence interval (CI).

Primary immunogenicity endpoints

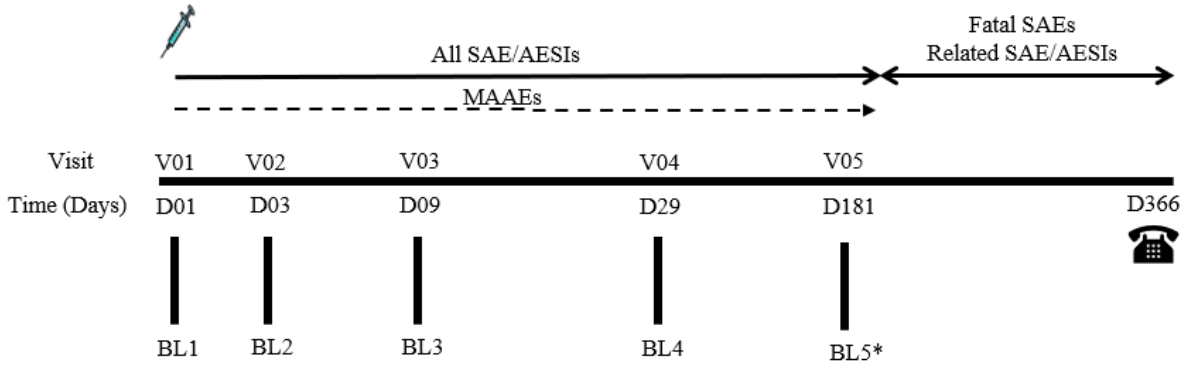
Immunogenicity endpoints will be described using 95% CI after injection in all groups according to the vaccine received and by age group (18-64 years and ≥ 65 years of age).

Independent Data Monitoring Committee: No

1.2 SCHEMA

The graphical design and schematic representation of the enrollment strategy of Study VAV00045 are presented in Figure 1 and Figure 2.

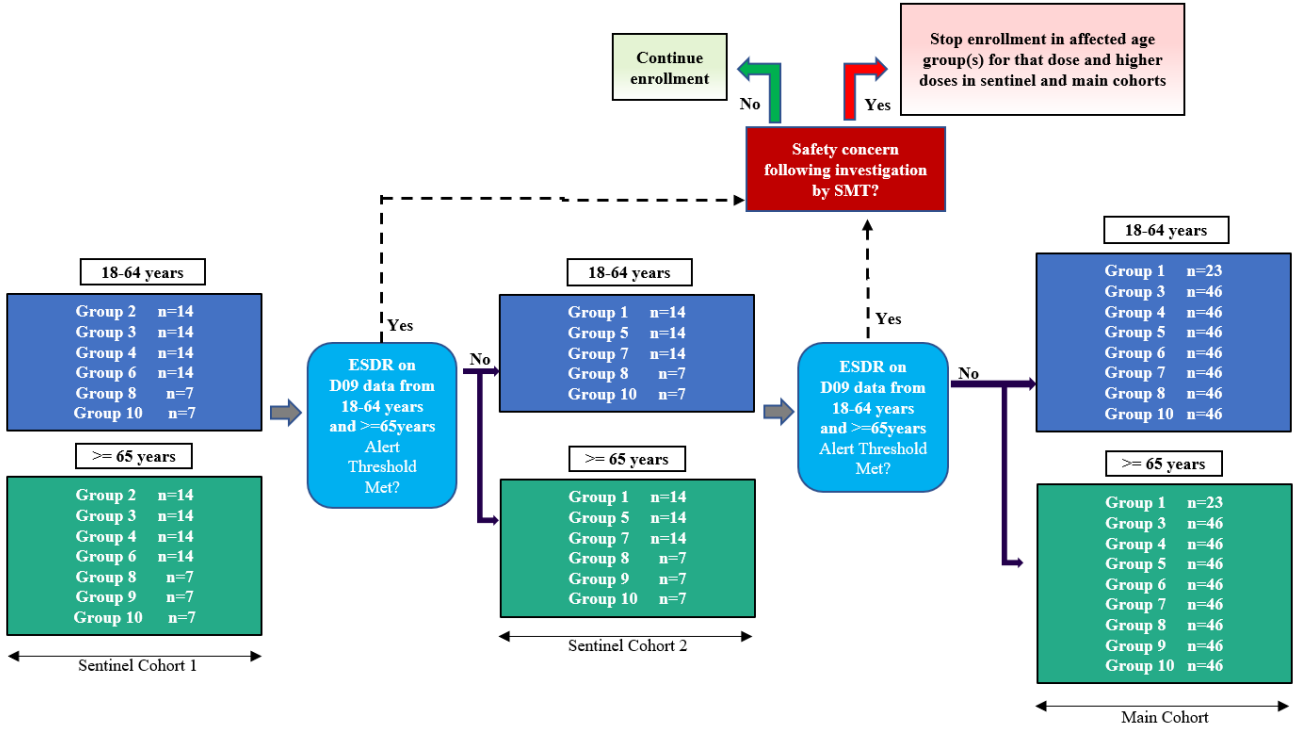
Figure 1: Graphical study design



*BL5 is taken only if participants did not receive a licensed seasonal influenza vaccine since V01

Abbreviations: AESI, adverse event of special interest; BL, Blood sample; D, day; MAAE, medically attended adverse event; SAE, serious adverse event; V, visit

Figure 2: Schematic representation of the enrollment strategy



ESDR, early safety data review; SMT, safety management team.

Group 1: QIV mRNA / [redacted] (MRT5421); Group 2: QIV mRNA / [redacted] (MRT5429); Group 3: QIV mRNA / [redacted] (MRT5429); Group 4: QIV mRNA / [redacted] (MRT5429); Group 5: QIV mRNA / [redacted] (MRT5429);Group 6: QIV mRNA / [redacted] (MRT5424); Group 7: QIV mRNA / [redacted] (MRT5424); Group 8: QIV-SD; Group 9: QIV-HD; Group 10: RIV4

Note: Participants aged 18-64 years and 65 years and older will be enrolled in parallel in the study. However, the enrollment of participants aged 18-64 years and 65 years and older may be done independently of each other in both sentinel and main cohorts; in that case, different ESDRs will be done to evaluate D09 data from either participants aged 18-64 years or 65 years and older (eg, up to 4 EDSRs can be done during the study).

1.3 SCHEDULE OF ACTIVITIES (SOA)

Table 5: Schedule of activities

Phase I / II Study, 5 Visits, 1 Phone Call, 1 Vaccination, 4 or 5 Blood Samples, 12 Months' Duration

Visit/Contact	***Collection of information in the eCRF***	**V01**	**V02**	**V03**	**V04**	**V05** [a]	**12-month follow-up phone call** [a]
Study timelines (days)		D01	D03	D09	D29	D181	D366
Time interval days			V01 + 2 days	V01 + 8 days	V01 + 28 days	V01 + 180 days	V01 + 365 days
Time windows (days)		NA	NA	[+2 D]	[+7 D]	[+14 D]	[+14 D]
Visit procedures:							
Informed consent	X	X					
Inclusion/exclusion criteria	X	X					
Collection of demographic data [b] (age, gender, race, and ethnicity)	X	X					
Serum or urine pregnancy test (if applicable) [c]		X					
Collection of medical history	X Significant Medical History	X					

[a] If any participants discontinue the study early (except the lost to follow-up), they are still to be followed up for safety and are to be contacted at D181 and D366 safety telephone call to identify the occurrence of any pregnancies, SAEs, and AESIs that had not yet been reported.

[b] To comply with US Food and Drug Administration expectations, Sponsors are to enroll participants who reflect the demographic for clinically relevant populations with regards to age, gender, race, and ethnicity (1) (2).

[c] In female participants of childbearing potential (ie, females who have not been postmenopausal for at least 1 year, nor are surgically sterile).

Visit/Contact	*Collection of information in the eCRF*	V01	V02	V03	V04	V05 [a]	12-month follow-up phone call [a]
Study timelines (days)		D01	D03	D09	D29	D181	D366
Time interval days			V01 + 2 days	V01 + 8 days	V01 + 28 days	V01 + 180 days	V01 + 365 days
Time windows (days)		NA	NA	[+2 D]	[+7 D]	[+14 D]	[+14 D]
History of seasonal influenza vaccination and lab-confirmed influenza illness [d]	X	X					
Full history of vaccination with mRNA vaccines	X	X					
Physical examination [e]		X	X	X	X	X	X
Pre-vaccination temperature		X					
Baseline electrocardiogram (ECG) [f]	X	X					
Measurement of vital signs [g]	X	X [h]	X	X	X		
Collection of concomitant medications	X Reportable concomitant medication	X					Influenza vaccination only
Contact IRT system for randomization, participant number and treatment allocation	X	X					
Blood sampling (BL)	X	X pre-vac	X	X	X	X[i]	

[d] History will be collected for the prior 3 influenza seasons.

[e] Full physical examination to be performed during V01. Targeted physical examination based on medical history may be performed at any other visit if needed.

[f] The physician's interpretation of ECG results will be recorded in the source and eCRF. Additional ECG will be performed as rapidly as possible (ie, at an unscheduled visit, if necessary) for any participant who develops symptoms of myocarditis, pericarditis, and/or myopericarditis during conduct of the study.

[g] Measurement of vital signs will include systolic blood pressure, diastolic blood pressure, and cardiac rhythm (heart rate).

[h] Vital signs will be measured before and 30 minutes after vaccination for all participants at V01.

[i] Blood sampling will only be performed for participants who did not receive a licensed seasonal influenza vaccine during study conduct.

Visit/Contact	***Collection of information in the eCRF***	**V01**	**V02**	**V03**	**V04**	**V05** [a]	**12-month follow-up phone call** [a]
Study timelines (days)		D01	D03	D09	D29	D181	D366
Time interval days			V01 + 2 days	V01 + 8 days	V01 + 28 days	V01 + 180 days	V01 + 365 days
Time windows (days)		NA	NA	[+2 D]	[+7 D]	[+14 D]	[+14 D]
Safety laboratory parameters [j]	X	X [k]	X [k]	X [l]			
Serum for antibodies (HAI, SN)		X			X	X	
Potential retesting and future research		X	X	X	X		
Vaccination (vac)	X	X					
Immediate surveillance (30 minutes)	X	X					
Participant diary provided [m]		X			X		
Participant diary reviewed (and collected if applicable) [n]			X	X	X	X	
Memory aid provided						X	
Collection of solicited injection site and systemic reactions	X	For 7 days after vaccination					
Collection of unsolicited AEs	X	For 28 days after vaccination					
Collection of MAAEs	X	For 180 days after vaccination					
Collection of SAEs (including AESIs)	X	All SAEs and AESIs				Fatal SAEs, and related SAE/AESIs	

[j] Safety laboratory assessments will include clinical chemistry (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total and direct bilirubin, C-reactive protein [CRP], and creatinine) and hematology (white blood cell [WBC] count with differential, hemoglobin, platelet count, and red blood cell [RBC] count). In case of abnormal safety laboratory results, unscheduled visits or additional laboratory assessments or procedures may occur based on Investigator's judgment to ensure the participant's safety.

[k] In addition to safety laboratory assessment performed at D01 and D03, troponin I testing will also be performed for screening for potential myocarditis cases.

[l] Troponin I will not be tested systematically at D09. Troponin I could be tested at D09 in case of abnormal values in previous samples.

[m] The Investigator or an authorized designee will remind the participants to bring back the participant diary at the next visit and will answer any questions.

[n] The Investigator or an authorized designee will interview the participants to collect the information recorded in the participant diary and will attempt to clarify anything that is incomplete or unclear.

Visit/Contact	***Collection of information in the eCRF***	**V01**	**V02**	**V03**	**V04**	**V05** [a]	**12-month follow-up phone call** [a]
Study timelines (days)		D01	D03	D09	D29	D181	D366
Time interval days			V01 + 2 days	V01 + 8 days	V01 + 28 days	V01 + 180 days	V01 + 365 days
Time windows (days)		NA	NA	[+2 D]	[+7 D]	[+14 D]	[+14 D]
Collection of pregnancies	X	To be reported at any time during the study					
Collection of End of Study Intervention Phase [o]	X				X		
Collection of Immunogenicity (for participants included into the Ab persistence) and collection of Safety Follow-up Phase (for all participants)	X					X	
Collection of 12-Month Follow-up – End of study	X						X

[o] In case of participant discontinuation at a visit, the entire visit will be completed.

2 INTRODUCTION

Sanofi Pasteur's quadrivalent influenza messenger ribonucleic acid (mRNA) vaccine is a novel vaccine that is being developed for preventing influenza.

2.1 STUDY RATIONALE

The objective of study VAV00045 is to evaluate the safety and immunogenicity of different formulations of quadrivalent influenza modified messenger ribonucleic acid vaccines (QIV mRNA), MRT5421, MRT5424, and MRT5429, administered as a single [redacted] in adult 18 years of age and older, compared to each other and to the 3 following active controls: standard-dose Fluzone® quadrivalent influenza vaccine (QIV-SD, Sanofi Pasteur [SP]) and Fluzone high-dose quadrivalent influenza vaccine (QIV-HD, SP), which will be a comparator for study participants ≥ 65 years of age only; or quadrivalent recombinant influenza vaccine (RIV4, SP).

2.2 BACKGROUND

Influenza is a contagious, acute viral respiratory disease caused by influenza type A and type B viruses. In adults, influenza is typically characterized by the rapid onset of fever, myalgia, sore throat, and non-productive cough, and can also cause severe malaise lasting for several days (3). While influenza affects all age groups, the infants, the elderly, and persons with underlying health problems are at increased risk for complications. Members of high-risk groups who become ill with influenza are more likely than the general population to require hospitalization (4).

Influenza-related complications in the adult population include primary viral pneumonia, secondary bacterial pneumonia, and/or exacerbation of underlying medical conditions, such as chronic obstructive pulmonary disease and congestive heart failure (5) (6).

Vaccination remains the most effective means of preventing influenza infection and complications associated with the disease (4). Currently, most influenza vaccines are generated in embryonated hen's eggs or in cell lines and contain hemagglutinin (HA) of each of the 4 virus strains (A/H1N1, A/H3N2, B/Yamagata lineage, and B/Victoria lineage influenza strains) recommended by the World Health Organization (WHO). Although well established, these processes take several months to manufacture a sufficient number of vaccine doses, and, in the case of egg-derived vaccines, rely on the availability of sufficient pathogen-free eggs and require adaptation of the virus to grow in eggs (7) (8). This can be a challenge for the development of vaccines against the influenza virus which regularly mutates through antigenic drift, and results in variants that can evade prior natural immunity (9). A change can occur more dramatically when there is re-assortment between mammalian and avian viruses leading to the emergence of novel strains with major changes in the HA antigen, in a process known as antigenic shift, which can lead to a pandemic outbreak, which requires a more rapid and large scale response for a timely vaccine solution (10). Hence, new and highly versatile approaches are required to quickly and effectively respond to these situations.

Messenger ribonucleic acid (mRNA) vaccines have the potential to be a promising alternative to conventional approaches. Once the antigen of choice from the targeted pathogen has been isolated, the antigen's gene is sequenced, synthesized, cloned into a deoxyribonucleic acid (DNA) template plasmid, and the mRNA is then produced by in vitro transcription (11). Once delivered into the participant, the mRNA is translated into the corresponding protein by the host cell machinery, allowing induction of both potent humoral and cellular immune responses. The fully synthetic nature of mRNA vaccines allows for the rapid development of virtually any antigen sequence, including those for new emerging targets, and the capacity to include multiple antigens in the same vaccine.

mRNA molecules are too large and negatively charged to passively cross the cell membrane, as well as being prone to nuclease degradation (12). Therefore, mRNA vaccines need a delivery system into host cells. Lipid nanoparticles (LNPs) are the most promising and commonly used tools for in vivo mRNA delivery (13). LNPs are usually composed of 4 components: 1) an ionizable cationic lipid promoting self-assembly in a circa 70 to 100 nm particle, encapsulating the mRNA and allowing its endosomal release, 2) a lipid-linked polyethylene glycol deposited preferentially on the LNP surface which increases the half-life of the formulation and reduces protein absorption, 3) cholesterol acting as a stabilizing agent, and 4) natural phospholipids supporting the lipid bilayer of the structure (10) (11) (14) (15). The mRNA-LNP vaccines are considered intrinsically immunogenic, thus obviating the need for additional adjuvant enhancement.

mRNA vaccines could bring significant advantages over traditional vaccines. These advantages include: 1) rapid development of new targets, 2) cell-free production without infectious elements used in their manufacturing process, 3) shorter manufacturing time, facilitating rapid response to strain changes and pandemic emergencies, and 4) potential to include multiple immunogens. In addition, mRNA is translated into protein by the human cell's own machinery in the cytoplasm and post-translationally modified, resulting in a properly folded protein for antigen presentation. Furthermore, mRNA vaccines are only targeted for cytoplasmic delivery circumventing the risk of genomic integration.

Sanofi has initiated a clinical development plan to develop a quadrivalent modified mRNA influenza vaccine (QIV mRNA) encoding the HA sequence of A/H1N1, A/H3N2, B/Yamagata lineage, and B/Victoria lineage influenza strains encapsulated in LNP.

Three Phase I / II dose ranging studies were designed to assess the safety and immunogenicity of different dose levels of QIV mRNA. Each dose level contained the same quantity for each mRNA encoding the HA sequence of 4 strains (ie, A:A:B:B ratio 1:1:1:1). Each of these studies assessed QIV modified mRNA encapsulated in LNP containing a different cationic lipid (Study VAV00002 with the [redacted], Study VAV00020 with the [redacted], and Study VAV00029 with the [redacted]) in comparison to licensed influenza vaccines in adults. All these 3 studies started in Q4 2022 and are currently ongoing.

[redacted]

[redacted]

A strategy for further development would be to evaluate a QIV mRNA vaccine candidate containing an unbalanced A:A:B:B ratio to improve the immune response against B strains by increasing the quantity of mRNA encoding the HA sequence of B influenza strains.

One of other lever which contributes to both immunogenicity and reactogenicity on QIV mRNA vaccines performance is the LNP.

Two LNPs with a different cationic lipid have showed promising data: [redacted], may lead to a better balance of immunogenicity and reactogenicity as compared to other LNPs based on nonclinical studies data (please refer to IB QIV mRNA / [redacted] for further details) and [redacted], with similar composition as Pfizer/BioNTech COVID vaccine, that is under evaluation in a Phase I study (Study VAV00019) with monovalent modified mRNA encoding the full-length HA sequence of A/Tasmania/503/2020 (H3N2) influenza virus encapsulated in [redacted]-based LNP (hereafter referred to as H3 mRNA / [redacted] vaccine) in healthy adults aged 18 to 49 years and 60 years and above in Australia and the UK. [redacted] who received the control RIV4 (licensed influenza vaccine) (all aged 18 to 49 years) showed that no major safety concerns were observed. In all groups, pain was the most reported injection site reaction, and headache, malaise, and myalgia were the most reported solicited systemic reactions. Most of the solicited reactions (injection site and systemic) were of Grade 1 or Grade 2, started within 3 days of injection, were present for 3 days or less, and resolved in most of cases without medication. No SAEs and adverse events of special interest (AESIs) were reported. In addition, the ongoing review of safety data for participants who received H3 mRNA / [redacted] showed that no safety concerns have been observed so far. In term of immunogenicity, the antibody response tended to be similar between H3 mRNA / [redacted] H3 mRNA / [redacted] and RIV4 (please refer to IB QIV / [redacted] for further details).

Therefore, the objective of the present study is to evaluate the safety and immunogenicity of different formulations of QIV mRNA vaccines containing an unbalanced ratio of mRNA encoding the HA sequence of A strains and B strains (A:A:B:B ratio 1:1:2:2) encapsulated in LNPs containing either [redacted] (MRT5421), [redacted] (MRT5429) or [redacted] (MRT5424) compared to each other and to licensed influenza vaccines in adults aged 18 years and above.

The goal of the study is to determine if QIV mRNA / [redacted] (MRT5429) or QIV mRNA / [redacted] (MRT5424), at the same dose or lower dose but the same A:A:B:B ratio as QIV mRNA / [redacted](MRT5421) improves the immunogenicity profile against A strains and B strains with comparable or improved safety.

2.3 BENEFIT/RISK ASSESSMENT

More detailed information about the known and expected benefits and risks, reasonably expected adverse events, the potential risks, and uncertainties of influenza mRNA vaccines may be found in the IBs). Details regarding the known and expected benefits and risks of the comparator vaccines can be found in the associated Product Information.

2.3.1 Risks from Study Participation

The potential risks of clinical significance and risk management are summarized in Table 6.

Table 6: Potential risks of clinical significance and risk mitigation / management

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Mitigation / Management
Investigated Vaccines: Quadrivalent Influenza mRNA vaccines (MRT5421, MRT5424, and MRT5429)		
Injection site reactions and systemic reactions	Potential adverse reactions (ARs) are expected to be similar to those observed for the mRNA vaccines assessed in different clinical studies; generally, injection site pain was the most commonly experienced injection site reaction, while headache, fatigue, myalgia, arthralgia, and chills were the most commonly experienced solicited systemic reactions (refer to the IB for further details).	During the informed consent process, the participants enrolling in the study will be informed of these potential reactions and the need to attend the clinic if they are unwell.
Anaphylactic reactions (including bronchospasms, and laryngeal spasms)	Potential risk All vaccines have the potential to cause allergic reactions or anaphylaxis in individuals who may be sensitized to components of the vaccine. Please refer to the IB for more information regarding the components of the vaccine.	Exclusion criterion E02 for those at increased risk. Observation period (30 minutes) after vaccination for early detection and treatment. Addressed in the IB (administration precautions, potential AEs), These events are SAEs or AESIs and will be collected until study end.
Guillain-Barré syndrome (GBS), neuritis (including Bell's palsy), convulsions, encephalitis, transverse myelitis, thrombocytopenia, and vasculitis	Potential risk Historically have been listed in the Core Company Data Sheet for inactivated influenza vaccines based largely on the reporting of isolated cases over decades of use.	During the informed consent process, the participants enrolling in the study will be informed of these potential risks and the need to attend the clinic if they are unwell. These events

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Mitigation / Management
	These are very rare events, and the available evidence has been insufficient to confirm, or exclude, a causal association.	are SAEs or AESIs and will be collected until study end.
Myocarditis / pericarditis / myopericarditis	Potential risk-based on the very rare risk identified from post-marketing surveillance of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) mRNA vaccines. Myocarditis or pericarditis have been reported in greatest numbers in males under the age of 30 years following a second dose of SARS-CoV-2 mRNA vaccines, but cases have been reported in older males and in females as well, and also following the first dose. It is unknown whether this risk could be linked to the mRNA technology or to the SARS-CoV-2 antigen (increased risk of myocarditis and pericarditis has also been identified following natural SARS-CoV-2 infection and after administration of non-mRNA SARS-CoV-2 vaccine). Please refer to the IB for further details.	Exclusion criteria (E03 and E04) for those with past or ongoing myocarditis and/or pericarditis. During the informed consent process, participants enrolling in the study will be informed of these potential risks and the need to attend the clinic if they are unwell. Each participant will have an electrocardiogram (ECG) at baseline and in the event of symptoms potentially compatible with myocarditis and/or pericarditis. In addition, troponin I will be tested pre- and post-vaccination to detect possible cases of myocarditis. Study participants with symptoms compatible with potential myocarditis/pericarditis will be referred to a consultation with a cardiologist or visit to the Emergency department as applicable. Cardiac adjudication Committee (CAC) will also evaluate such cases. These events are AESIs and will be collected until study end.
Persons at Risk of Bleeding	As with other [redacted] QIV mRNA should be given with caution in individuals with bleeding disorders, such as hemophilia or on anticoagulant therapy, to avoid the risk of hematoma following the injection.	Exclusion criterion E06 for those at increased risk

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Mitigation / Management
Comparator: QIV-SD **(To refer to Fluzone Quadrivalent vaccine Product Information)**		
Anaphylactic reactions (including bronchospasms, and laryngeal spasms)	All vaccines have the potential to cause allergic reactions or anaphylactic reactions in individuals who may be sensitized to components of the vaccine. Please refer to the Product Information for more information regarding the components of the vaccine.	Exclusion criterion E02 for those at increased risk. Observation period (30 minutes) after vaccination for early detection and treatment. Addressed in Product Information (administration precautions, potential AEs). These events are SAE or AESI and will be collected until study end.
Injection site reactions and systemic reactions	The following data are from the Package Insert of Fluzone Quadrivalent influenza vaccine. In adults 18 years and older, the most common (≥10%) injection site reaction was pain (47%); the most common solicited systemic ARs were myalgia (24%), headache (16%), and malaise (11%). In adults 65 years of age and older, the most common (≥10%) injection site reaction was pain (33%); the most common solicited systemic ARs were myalgia (18%), headache (13%), and malaise (11%).	During the informed consent process, the participants enrolling in the study will be informed of these potential reactions and the need to attend the clinic if they are unwell.
GBS, neuritis (including Bell's palsy), convulsions, encephalitis, transverse myelitis, thrombocytopenia, and vasculitis	Historically have been listed in the Core Company Data Sheet for inactivated influenza vaccines based largely on the reporting of isolated cases over decades of use. Very rare events and the available evidence have been insufficient to confirm, or exclude, a causal association.	During the informed consent process, the participants enrolling in the study will be informed of these potential risks and the need to attend the clinic if they are unwell. This event is SAE or AESI and will be collected until study end.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Mitigation / Management
Persons at Risk of Bleeding	As with other [redacted] QIV-SD should be given with caution in individuals with bleeding disorders, such as hemophilia or on anticoagulant therapy, to avoid the risk of hematoma following the injection.	Exclusion criterion E06 for those at increased risk.
Comparator: QIV-HD **(To refer to Fluzone High-Dose Quadrivalent vaccine Product Information)**		
Anaphylaxis	Identified risk: All vaccines have the potential to cause allergic reactions or anaphylaxis in individuals who may be sensitized to components of the vaccine. Please refer to the Product Information for more information regarding the components of the vaccine.	Exclusion criterion E02 for those at increased risk. Observation period (30 minutes) after vaccination for early detection and treatment. Addressed in Product Information (administration precautions, potential AEs), defined as AESI in the study.
Injection site reactions and systemic reactions	The following data are from the Package Insert of Fluzone High-Dose Quadrivalent influenza vaccine. In adults 65 years of age and older, the most common (≥◦10%) injection site reaction was pain (41%); the most common (≥◦10%) solicited systemic ARs were myalgia (23%), headache (14%), and malaise (13%).	During the informed consent process, the participants enrolling in the study will be informed of these potential reactions, the need to attend the clinic if they are unwell, and the possibility to take analgesic / antipyretic drug.
GBS, neuritis (including Bell's palsy), convulsions, encephalitis, transverse myelitis, thrombocytopenia, and vasculitis	Potential risk: Historically have been listed in the Core Company Data Sheet for inactivated influenza vaccines based largely on the reporting of isolated cases over decades of use. Very rare events and the available evidence have been insufficient to confirm, or exclude, a causal association.	During the informed consent process, the participants enrolling in the study will be informed of these potential risks and the need to attend the clinic if they are unwell. Except for thrombocytopenia (monitored as part of safety laboratory assessment), these events are SAE or AESI and will be collected until study end.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Mitigation / Management
Comparator: RIV4 **(To refer to Flublok Quadrivalent vaccine Product Information)**		
Anaphylaxis	Identified risk: All vaccines have the potential to cause allergic reactions or anaphylaxis in individuals who may be sensitized to components of the vaccine. No case of anaphylaxis was reported as related to Flublok vaccine during the clinical development. Adverse events (immune system disorders) have been spontaneously reported during post-approval use of Flublok Quadrivalent. Please refer to the Product Information for more information regarding the components of the vaccine and data from previous experience with the Flublok Quadrivalent vaccine.	Exclusion criterion E02 for those at increased risk. Observation period (30 minutes) after vaccination for early detection and treatment. Addressed in the Product Information (administration precautions, potential AEs).
Injection site reactions and systemic reactions	The following data are from the Package Insert of Flublok Quadrivalent influenza vaccine. In adults 18 through 49 years of age, the most common (≥ 10%) injection site reactions were tenderness (48%) and pain (37%); the most common (≥ 10%) solicited systemic ARs were headache (20%), fatigue (17%), myalgia (13%) and arthralgia (10%). In adults 50 years of age and older, the most common (≥10%) injection site reactions were tenderness (34%) and pain (19%); the most common (≥10%) solicited systemic ARs were headache (13%) and fatigue (12%).	During the informed consent process, the participants enrolling in the study will be informed of these potential reactions, the need to attend the clinic if they are unwell, and the possibility to take antalgic / antipyretic drug.
GBS	No cases of GBS were reported as related to Flublok Quadrivalent vaccine during the clinical development. However, cases of GBS have been spontaneously	During the informed consent process, the participants enrolling in the study will be informed of this potential risk and the need to attend the clinic

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Mitigation / Management
	reported during post-approval use of Flublok Quadrivalent vaccine. A causal association between these cases of GBS and Flublok Quadrivalent vaccine has not been established	if they are unwell. GBS is an AESI and will be collected until study end.
Study Procedures		
Vasovagal reactions (syncope), or psychogenic reactions to needle (vaccine injection or blood sampling)	Anxiety-related reactions can occur following, or even before, any vaccination as a psychogenic response to the needle injection or blood draw, and may be accompanied by several neurological signs such as transient visual disturbance, paresthesia, or seizure-like activity	Observation period (30 min) after vaccination for early detection and treatment.
Theoretical risk that participant can be exposed to SARS-CoV-2 infected individuals	SARS-CoV-2 infection is highly contagious. SARS-CoV-2 spreads through respiratory secretion or droplets. Transmission may also be possible via contaminated surfaces. Exposure can theoretically occur as a result of study procedures, including visits to the investigational sites and physical interactions with study staff.	Study sites are to set up appropriate infection control measures to prevent participants from getting exposed during the study visits. Participants contact with other individuals when visiting study site (study site to set up system) should be minimized. Protective material (eg, masks and gowns) to be used at the sites. Home visit option for completion of study procedures in the setting of containment measures to minimize exposure (see Section 10.6).

Appropriate medical equipment and routine emergency medications must be available on-site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction. This equipment is not provided by the Sponsor.

2.3.2 Benefits from Study Participation

Although there is some evidence in preclinical and clinical studies that being vaccinated with the QIV mRNA vaccine induce immune responses against influenza strains, there is no guarantee that participants get any benefit from it.

However, they will benefit from medical evaluations/assessments associated with study procedures (eg, medical visits, physical exam, laboratory parameter assessment, etc.) participants will contribute to the process of developing a new kind of vaccine (mRNA vaccine) that may improve existing vaccines.

2.3.3 Overall Benefit-Risk Conclusion

Considering the measures taken to minimize risk to participants enrolled in this study, there is no unreasonable and significant risk of illness or injury for the participants.

3 OBJECTIVES AND ENDPOINTS

The study objectives and the corresponding endpoints are described in Table 7.

Table 7: Objectives and endpoints

Objectives	Endpoints
Primary	
Safety objective • To describe the safety profile of each QIV mRNA compared to each other and to QIV-SD, RIV4, or QIV-HD* in all participants and in each age group	***Safety endpoints*** • Presence of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after injection • Presence of solicited injection site reactions (ie, pre-listed in the participant diary and in the case report form [CRF]) occurring up to 7 days after injection • Presence of solicited systemic reactions (ie, pre-listed in the participant diary and in the CRF) occurring up to 7 days after injection • Presence of unsolicited AEs reported up to 28 days after injection • Presence of medically attended adverse events (MAAEs) reported up to 180 days after injection • Presence of SAEs and AESIs throughout the study • Presence of out-of-range biological test results (including shift from baseline values) up to 8 days after injection[†]

Immunogenicity objective
• To describe the HAI immune response induced by each QIV mRNA compared to each other and to QIV-SD, RIV4, or QIV-HD* in all participants and in each age group
	Immunogenicity endpoints
	• HAI antibody (Ab) response to each homologous strain at Day (D)29:
	  • HAI titers at D01 and D29
	  • Detectable HAI titer (HAI titer ≥ 10 [1/dil]) at D01 and D29
	  • Individual HAI Ab titer ratio D29/D01
	  • Seroconversion (HAI Ab titer < 10 [1/dil] at D01 and post-injection titer ≥ 40 [1/dil] at D29, or titer ≥ 10 [1/dil] at D01 and a ≥ 4-fold increase in titer [1/dil] at D29)

	• HAI Ab titer ≥ 40 (1/dil) at D29 • 2-fold and 4-fold rise in HAI titers from D01 to D29
Secondary	
• To describe the neutralizing Ab immune response induced by each QIV mRNA compared to each other and to QIV-SD, RIV4, or QIV-HD* in all participants and in each age group	• Neutralizing Ab response to each homologous strain at D29 • Neutralizing Ab titers at D01 and D29 • Individual neutralizing antibodies titer ratio D29/D01 • 2-fold and 4-fold increase in neutralizing titers from D01 to D29
Exploratory	
[redacted]	[redacted]

[redacted]

† Safety laboratory assessments will include serum chemistries (liver enzymes including aspartate aminotransferase [AST], alanine aminotransferase [ALT], total and direct bilirubin, C-reactive protein (CRP), creatinine); hematology (white blood count [WBC] with differential, hemoglobin, platelet count, and red blood cell [RBC] count); and troponin I (for screening for potential myocarditis cases, systematically tested at D01 and D03, and at D09 only in case of abnormal values in previous samples).

4 STUDY DESIGN

4.1 OVERALL DESIGN

The design of the study is summarized in Table 8.

Table 8: Overall design

Type of design	Parallel, with dose-escalation for sentinel cohort, multi-center
Phase	I / II
Control method	Active-controlled (control = QIV-SD; QIV-HD [adults ≥ 65 years of age only]; RIV4)
Study population	Adults 18 years of age and older
Level and method of blinding	Modified double-blind (sentinel and main cohorts) (Participants; Sites except for those preparing/administering study intervention; Sponsor's except Sponsor unblinded internal safety review committee)
Investigational intervention assignment method	Randomization
Number of participants	Up to 1002 participants (471 participants 18-64 years of age and 531 participants ≥ 65 years of age)
Intervention groups	Sentinel safety cohort 1: up to 147 participants (up to 70 participants aged 18-64 years and up to 77 participants aged 65 years and above) Sentinel safety cohort 2: up to 119 participants (up to 56 participants aged 18-64 years and up to 63 participants aged 65 years and above) The enrollment of participants will be performed in a stepwise manner, based on the successful early safety data reviews (ESDRs) performed by an internal Sponsor core Safety Management Team (SMT). Further details on the sequential enrollment of cohorts and ESDRs are presented in Section 8.4.9. Main cohort: up to 736 participants (up to 345 participants aged 18-64 years and up to 391 participants aged 65 years and above)
Total duration of study participation	Approximately 12 months
Countries	US, Puerto Rico, Honduras
Use of an Independent Data Monitoring Committee, Dose Escalation Committee, or similar review group	Independent Data Monitoring Committee: No Sponsor's internal safety management team (SMT): Yes External cardiac adjudication committee (CAC): Yes

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Rationale for Study Population

It is proposed to undertake this Phase I / II study in adults in both younger and older age groups (adults 18-64 years of age and 65 years of age and older, respectively). While the younger population is also vulnerable to influenza disease, the burden of influenza is highest in the older age groups and vaccine effectiveness is lower in older populations. Thus, there is a need to generate improved vaccines for both young and older adults. Both age groups are evaluated in the Phase I / II study to be able to generate early data on the safety and immune response of these different QIV mRNA vaccines encapsulated in LNPs containing either [redacted] in each age group, as it is possible that the dose used for the vaccine may be different for each age group. All sites will target to have community outreach programs to ensure that ethnic and racial diversity will be, at a minimum, representative of the population of the countries in which the study is being conducted.

Rationale for Control

QIV-SD will serve as a reference control, while QIV-HD and RIV4 will be used as benchmark controls in the study. QIV-HD is proposed as a comparator from a reactogenicity standpoint, as QIV-HD induces higher reactogenicity than QIV-SD; therefore, reactogenicity of different doses of the QIV mRNA / [redacted] against QIV-HD may provide an early data point for decision-making in the older age group. In contrast to QIV-SD and QIV-HD, which are egg-based vaccines, RIV4 contains the exact HA sequence of each strain (ie, no egg adaptations) and does not contain neuraminidase or nucleoprotein antigens.

Rationale for Enrollment in Stepwise Manner

Participants ≥ 65 years of age will be enrolled in parallel to the enrollment of participants 18-64 years of age in sentinel cohorts as safety data generated in clinical trials and post-authorization studies with mRNA vaccines showed that older adults generally exhibit lower reactogenicity profiles compared to younger adults (16) (17) (18) and safety data from Study VAV00020 with QIV mRNA / [redacted] in adults 18 years of age and older confirmed this observation (see IB QIV mRNA /[redacted] for further details).

As a safety precaution, a few numbers of participants aged 18-64 years and 65 years and older participants will be first randomized to receive a single [redacted] of either QIV mRNA / [redacted] QIV mRNA /[redacted], QIV mRNA / [redacted], QIV mRNA / [redacted] or control (RIV4, QIV-SD or QIV-HD [adults ≥ 65 years of age only]) in sentinel cohort 1. If there is no safety concern, QIV mRNA / [redacted], QIV mRNA / [redacted] QIV mRNA / [redacted], or controls will be administered to participants in sentinel cohort 2. If there is no safety concern, then a larger number of participants will be enrolled into the main cohort.

All D01 to D09 safety data of each participant of the sentinel cohorts will be closely monitored by the internal Sponsor core SMT. An ESDR is planned following each sentinel cohort once safety data have been collected through D09 after vaccination, as well as cumulative safety data for previous cohorts, if available (see Figure 2 for the enrollment strategy and Section 8.4.9 for ESDR

details). In addition, in the event that a participant develops symptoms of myocarditis, pericarditis, and / or myopericarditis, cardiac monitoring data will be assessed by an external CAC.

Of note, in case of enrollment issue, participants aged 18-64 years and 65 years and older may be enrolled independently of each other in both sentinel and main cohorts; in that case, different ESDRs will be done to evaluate D09 data from either participant aged 18-64 years or 65 years and older.

4.3 JUSTIFICATION FOR DOSE

QIV mRNA / [redacted]

[redacted]

QIV mRNA / [redacted]

[redacted]

[redacted]

QIV mRNA / [redacted]

[redacted]

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if the participant has completed the last contact planned in the Schedule of Activities (SoA).

The end of the study is defined as the date of the last test results have been released for samples collected at Visit 04 (D29), related to primary and secondary endpoints. The end of the study must be achieved no later than 9 months after the last contact of the last participant in the study.

However, for periodic safety reports, the study is considered completed when the clinical study report is finalized.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible for the study only if all of the following criteria are met:

Age

I 01. Aged from 18 years on the day of inclusion[a] or aged from 21 years on the days of inclusion[b], depending on the countries.

Sex, contraceptive/barrier method and pregnancy testing requirements

I 02. A female participant is eligible to participate if she is not pregnant or breastfeeding and one of the following conditions applies:

- Is of non-childbearing potential. To be considered of non-childbearing potential, a female must be postmenopausal for at least 1 year, or surgically sterile.

  OR
- Is of childbearing potential and agrees to use an effective contraceptive method or abstinence from at least 4 weeks prior to study intervention administration until at least 12 weeks after study intervention administration.

A female participant of childbearing potential must have a negative highly sensitive pregnancy test (urine or serum as required by local regulation) within 8 hours before the 1st dose of study intervention.

Informed Consent

I 03. Informed consent form has been signed

Other Inclusions

I 04. Able to attend all scheduled visits and to comply with all study procedures

[a] "18 years" means from the day of the 18th birthday, for participants in US
[b] "21 years" means from the day of the 21st birthday for participants in Puerto Rico and Honduras

5.2 EXCLUSION CRITERIA

Participants are not eligible for the study if any of the following criteria are met:

Medical conditions

E 01. Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)

E 02. Known systemic hypersensitivity to any of the study intervention components (eg, polyethylene glycol, polysorbate); history of a life-threatening reaction to the study interventions used in the study or to a product containing any of the same substances; any allergic reaction (eg, anaphylaxis) after administration of mRNA vaccine

E 03. Previous history of myocarditis, pericarditis, and / or myopericarditis

E 04. Known history of previous episodes of Gillian-Barre Syndrome, neuritis (including Bell's palsy), convulsions, encephalitis, transverse myelitis, and vasculitis

E 05. Participants with an electrocardiogram (ECG) that is consistent with possible myocarditis or pericarditis or, in the opinion of the investigator, demonstrates clinically relevant abnormalities that may affect participant safety or study results

E 06. Self-reported thrombocytopenia, contraindicating IM injection based on Investigator's judgment

E 07. Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating IM injection based on Investigator's judgment

E 08. Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with study conduct or completion[c]

E 09. Moderate or severe acute illness / infection (according to investigator's judgment) or febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]) on the day of study intervention administration. A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided

E 10. Alcohol, prescription drug, or substance abuse that, in the opinion of the Investigator, might interfere with the study conduct or completion

E 11. Participant who had acute infection symptoms or a positive SARS-CoV-2 RT-PCR or antigen test in the past 10 days prior to the first visit (V01)

[c] Chronic illness may include, but is not limited to, cardiac disorders, renal disorders, auto-immune disorders, diabetes, psychiatric disorders, or chronic infection

Prior/concomitant therapy

E 12. Receipt of any vaccine in the 4 weeks preceding study intervention administration or planned receipt of any vaccine in the 4 weeks following study intervention administration[d]

E 13. Receipt of immune globulins, blood or blood-derived products in the past 3 months

E 14. Previous vaccination against influenza in the previous 6 months with an investigational or marketed vaccine

E 15. Receipt of any mRNA vaccine/product in the 2 months preceding study intervention administration

Prior/concurrent clinical study experience

E 16. Participation at the time of study enrollment (or in the 4 weeks preceding the study intervention administration) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure

Other exclusions

E 17. Self-reported or documented seropositivity for human immunodeficiency virus, hepatitis B virus, or hepatitis C virus

E 18. Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily

E 19. Any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives, including planning to leave the area of the study before the end of the study or participation in strenuous or endurance exercise through V03

E 20. Identified as an investigator or employee of the investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (ie, parent, spouse, natural or adopted child) of the investigator or employee with direct involvement in the proposed study

If the participant has a primary physician who is not the investigator, the site may contact this physician with the participant's consent to inform him / her of the participant's participation in the study. In addition, the site should ask this primary physician to verify exclusion criteria relating to previous therapies, such as receipt of blood products or previous vaccines.

[d] If the participant is enrolled and seeks vaccination of an authorized influenza vaccine or COVID-19 vaccine outside of the study, he / she will be encouraged to discuss this intention proactively with the study investigator and will be permitted to receive the authorized vaccine at the earliest 28 days after study vaccination and at any time thereafter. If the participant receives the authorized influenza vaccine or COVID-19 vaccine, this information will be collected. Participants will continue to be followed up for the duration of the study as per scheduled visits and procedures

5.3 LIFESTYLE CONSIDERATIONS

No other restrictions than the ones listed in the exclusion criteria or in the contraindications for subsequent vaccinations are required.

5.4 SCREEN FAILURES

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently assigned to study intervention. Screening information is recorded in the source documents.

Individuals who do not meet the criteria for participation in this study (screen failure) cannot be rescreened.

5.5 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT/RANDOMIZATION/ADMINISTRATION OF STUDY INTERVENTION

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures proposed in Appendix 10.6: Contingency measures for a regional or national emergency that is declared by a governmental agency should be considered for enrollment/randomization/administration of study intervention.

6 STUDY INTERVENTIONS AND CONCOMITANT THERAPY

Study interventions are all pre-specified, investigational and non-investigational/auxiliary medicinal products, medical devices and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

Note: Vaccines or products administered outside of study protocol are not considered as study interventions and are reported in the CRF as reportable medications (see Section 6.9). Study procedures (eg, blood sampling) are also not considered as study interventions.

6.1 STUDY INTERVENTIONS ADMINISTERED

Study interventions are described in Table 9 and Table 10.

Table 9: Identity of experimental study interventions

Group Number	1	2	3	4	5	6	7
Group Name	QIV mRNA [redacted] (MRT5421)	QIV mRNA [redacted]					QIV mRNA [redacted] (MRT5424)
Intervention Name	QIV mRNA [redacted] NH22/23	QIV mRNA [redacted] NH22/23				QIV mRNA [redacted] NH22/23	
Use	Experimental	Experimental	Experimental	Experimental	Experimental	Experimental	Experimental
IMP or NIMP/AxMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP
Type	Vaccine	Vaccine	Vaccine	Vaccine	Vaccine	Vaccine	Vaccine
Presentation		Suspension for injection in a vial					
Formulation / Dosage	[redacted] QIV mRNA MRT5421 per dose (LNP [redacted]): quantities of full-length of HA mRNA from each strain of 2022-2023 NH strains: [redacted]	[redacted] QIV mRNA MRT5429 per dose (LNP [redacted]): quantities of full-length of HA mRNA from each strain of 2022-2023 NH strains:	[redacted] QIV mRNA MRT5429 per dose (LNP [redacted]): quantities of full-length of HA mRNA from each strain of 2022-2023 NH strains:	[redacted] QIV mRNA MRT5429 per dose (LNP [redacted]): quantities of full-length of HA mRNA from each strain of 2022-2023 NH strains: [redacted]	[redacted] QIV mRNA MRT5429 per dose (LNP [redacted]): quantities of full-length of HA mRNA from each strain of 2022-2023 NH strains: [redacted]	[redacted] QIV mRNA MRT5424 per dose (LNP [redacted]): quantities of full-length of HA mRNA from each strain of 2022-2023 NH strains: [redacted]	[redacted] QIV mRNA MRT54254 per dose (LNP [redacted]): quantities of full-length of HA mRNA from each strain of 2022-2023 NH strains: [redacted]

Excipient / Diluent	[redacted]						
IMP preparation							
Dosage Level							
Number of Doses / Dosing Interval							
Route of Administration							
Site of Administration							
Sourcing	Provided by the Sponsor	Provided by the Sponsor	Provided by the Sponsor	Provided by the Sponsor	Provided by the Sponsor	Provided by the Sponsor	Provided by the Sponsor
Packaging and Labeling	Each vial will be labeled and packed in separate boxes (mRNA and diluents) due to the temperature differences. Each vial and each box will bear fixed label containing the dose number. All will be labeled as required per country requirement.						
Storage Conditions	[redacted]						

AxMP, auxiliary medicinal product; [redacted] IMP, investigational medicinal product; NH, Northern hemisphere; NIMP, non-investigational medicinal product; PBS, phosphate-buffered saline

Table 10: Identity of control study interventions

Group Number	8	9	10
Intervention Name	QIV-SD (Fluzone Quadrivalent vaccine) NH22/23	QIV-HD (Fluzone high-dose quadrivalent influenza vaccine) NH22/23	RIV4 (Flublok Quadrivalent vaccine) NH22/23
Use	Active control	Active control	Active control
IMP or NIMP/AxMP	IMP	IMP	IMP
Type	Vaccine	Vaccine	Vaccine
Dose Form	Suspension for injection in pre-filled syringe	Suspension for injection in pre-filled syringe	Solution for injection in pre-filled syringe
Formulation / Dosage	[redacted] HA per dose: [redacted] of HA per strain from 2022-2023 NH strains	[redacted] HA per dose: [redacted] of HA per strain from 2022-2023 NH strains	[redacted] HA per dose: [redacted] of HA per strain from 2022-2023 NH strains
Dosage Level	[redacted]		
Number of Doses / Dosing Interval			
Route of Administration			
Site of Administration			
Sourcing	Provided by the Sponsor	Provided by the Sponsor	Provided by the Sponsor
Packaging and Labeling	Each study intervention will be provided in a pre-filled syringe for direct injection. Each syringe and each box will bear fixed label containing the dose number. All will be labeled as required as per country requirement.		
Storage Conditions	[redacted]		

AxMP, auxiliary medicinal product; [redacted] IMP, investigational medicinal product; NH, Northern hemisphere; NIMP, non-investigational medicinal product

Table 11 summarized the study interventions per arm.

Table 11: Study Arms

Arm title	Gp 1	Gp 2	Gp 3	Gp 4	Gp 5	Gp 6	Gp 7	Gp 8	Gp 9	Gp 10
Arm type	Exp	Exp	Exp	Exp	Exp	Exp	Exp	Cont.	Cont.	Cont.
Associated group name	QIV mRNA [redacted] (MRT5421)	QIV mRNA [redacted] (MRT5429)	QIV mRNA [redacted] (MRT5429)	QIV mRNA [redacted] (MRT5429)	QIV mRNA [redacted] (MRT5429)	QIV mRNA [redacted] (MRT5424)	QIV mRNA [redacted] (MRT5424)	QIV-SD	QIV-HD	RIV4

Cont, control; Exp, experimental; Gp, group

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

1) The investigator or designee must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2) Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, or administer study intervention.
3) All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
4) The investigator, institution, the head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
5) Further guidance and information for the final disposition of unused study interventions will be provided to the study personnel.

6.3 ASSIGNMENT TO STUDY INTERVENTION

On the day of enrollment, participants who meet all the inclusion criteria but none of the exclusion criteria and sign the informed consent form (ICF) will be randomly assigned to either QIV mRNA groups, QIV-SD, RIV4, or QIV-HD (only for participants aged 65 years and above) in a ratio of allocation between 2 groups as [redacted]. Randomization will be stratified according to cohort and age group, and for the main cohort also stratified on previous year influenza vaccination status. The randomization will be generated using block method. Further details will be presented in the Interactive Response Technology (IRT) specifications.

Site staff will connect to the IRT enter the identification and security information, and confirm a minimal amount of data in response to IRT prompts. The IRT will then provide the group assignment and have the site staff confirm it. If the participant is not eligible to participate in the study, then the information will only be recorded on the participant recruitment log.

[redacted]

6.4 BLINDING

The study will be performed in a modified double-blind fashion:

- Investigators and study staff who conduct the study assessment, the participant and Sponsor (except Sponsor's unblinded internal safety review committee) will not know which study intervention is administered
- Only the study staff who prepare and administer the study intervention and Sponsor staff involved in SMT will know which study intervention is administered

The code may be broken in the event of an AE only when the identification of the study intervention received could influence the treatment of the participant. Code-breaking should be limited to the participant(s) experiencing the AE.

The blind can be broken by the investigator or a designee through the IRT system. Once the emergency has been addressed by the site, the investigator or a designee must notify the Sponsor's Responsible medical officer (RMO) if a participant's code was broken. All contact attempts with the Sponsor prior to unblinding are to be documented in the source documents, and the code-breaking CRF is to be completed.

The Independent Ethics Committees (IEC) / Institutional Review Boards (IRB) must be notified of the code-breaking, in accordance with local regulations. All documentation pertaining to the event must be retained in the site's study records and in the Sponsor's files. Any intentional or unintentional code-breaking must be reported, documented, and explained, and the name of the person who requested it must be provided to the Sponsor.

A request for the code to be broken may also be made:

- by the Global Pharmacovigilance (GPV) Department through an internal system for reporting to Health Authorities in the case of an unexpected SAE considered causally related, as described in International Council for Harmonisation (ICH) E2A. In this case, the code will be broken only for the participant(s) in question. The information resulting from code-breaking (ie, the participant's study intervention or group assignment) will not be communicated to either the investigator or the immediate team working on the study, except for the GPV representative.

6.5 STUDY INTERVENTION COMPLIANCE

The following measures will ensure that the study intervention is administered as planned (see Table 9 and Table 10), and that any noncompliance is documented so that it can be accounted for in the data analyses:

- All study interventions will be administered by qualified and trained study personnel
- The person in charge of study intervention management at the site will maintain accountability records of study intervention delivery to the study site, study intervention inventory at the site, dose(s) given to each participant, and unused or wasted doses

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in

Appendix 10.6: Contingency Measures for a regional or national emergency that is declared by a governmental agency.

6.6 DOSE MODIFICATION

Not applicable.

6.7 CONTINUED ACCESS TO STUDY INTERVENTION AFTER THE END OF THE STUDY

Not applicable.

6.8 TREATMENT OF OVERDOSE

Since the study intervention is administered by a health care professional, it is unlikely that overdose by injection occurs.

However, in the event of an overdose, the investigator should:

1) Contact the RMO immediately.
2) Closely monitor the participant for any AE/SAE.
3) Document the quantity of the excess of the overdose in the source documents.

See also Section 8.4.8 for the reporting.

6.9 PRIOR AND CONCOMITANT THERAPY

Prior and concomitant therapy collected includes medications that may affect the interpretation of safety data (eg, an antipyretic or analgesic that could have reduced the intensity or frequency of an adverse event) or may interfere with the development or measurement of the immune response (eg, the use of immune-suppressors, immune-modulators, or some antibiotics that can affect certain bioassays). Some medications such as steroids can affect both the evaluation of the safety and the immune response to a vaccine.

This may include medications of interest that were started prior to the day of vaccination, and even stopped prior to enrollment if there is a reasonable possibility that they may have an impact on safety and / or immune assessment during study participation.

The following reportable medications are defined:

- Medications impacting or that may have an impact on the evaluation of the safety (eg, antipyretics, analgesics, and non-steroidal anti-inflammatory drugs [NSAIDs], systemic steroids/corticosteroids)
  Note: Topical analgesics should NOT be applied at the injection site of study intervention; however, if they are applied inadvertently, they should be recorded.
- Medications impacting or that may have an impact on the immune response (eg, other vaccines, blood products, antibiotic classes that may interfere with bioassays used by the Sponsor's laboratory or other testing laboratories, systemic steroids/corticosteroids,

immune-suppressors, immune-modulators with immunosuppressive properties, anti-proliferative drugs such as DNA synthesis inhibitors)
- Medications impacting or that may have an impact on both the safety and the immune response (eg, systemic steroids/corticosteroids)

Reportable medications will be collected in the CRF until the end of the 6-months follow-up. History of influenza vaccination during the past 3 years will be collected in the CRF prior to the vaccination and seasonal influenza vaccine received during the study will be collected in the CRF until the end of 12-month follow-up.

Reason for treatment, route, dose, frequency, homeopathic medication, topical and inhaled steroids, as well as topical, ophthalmic, and ear treatments will not be recorded (except topical analgesics applied at the injection site of study intervention).

Medications given in response to an AE will be captured in the "Action Taken" section of the AE CRF only. No details will be recorded in the concomitant medication Form of the CRF unless the medication(s) received belong(s) to the reportable medications list. Medications will be coded using the WHO Drug dictionary.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 10.1.9.

7.1 DISCONTINUATION OF STUDY INTERVENTION

Not applicable as there is only one vaccination.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at the participant's own request, for any reason (or without providing any reason).
- A participant may be withdrawn from the study at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.
- The reason for withdrawal should be clearly documented in the source documents and in the CRF.
- The participant will be permanently discontinued from the study intervention and the study at that time. However, the site should attempt to contact the participant and complete all scheduled safety follow-ups, except if the participant specified that they do not want to be contacted again and it is documented in the source document.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested (unless local law requires not to destroy them), and the investigator must document this in the site study records.
- Withdrawn participants will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and the participant is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the site for a required study visit or if the participant cannot be contacted as planned in the SoA:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the Sponsor or the investigator, as per local health authority/ethics requirements (see Appendix 10.6).
- Laboratory that could unblind the study will not be reported to sites or other blinded personnel until the study has been unblinded.

8.1 ADMINISTRATIVE AND GENERAL PROCEDURES

8.1.1 Medical History

Prior to enrollment, participants will be assessed for pre-existing conditions and illnesses, both past and ongoing. Any such conditions will be documented in the source document. Significant (clinically relevant) medical history (reported as diagnosis) including conditions/illnesses for which the participant is or has been followed by a physician or conditions/illnesses that could resume during the course of the study or lead to an SAE or to a repetitive outpatient care will be collected in the CRF. Collected information will be coded using the Medical Dictionary for Regulatory Activities (medDRA).

In addition, history of vaccination with mRNA vaccines, history of seasonal of influenza vaccination and influenza diagnosis will also be recorded.

8.1.2 Sample Collection

Urine and blood samples will be collected as described in the SoA table (Section 1.3).

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 125 mL, see Table 12. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 12: Blood sampling volume (mL) per visit

Visit Number (V) **Study timelines (days)** **Time windows (days)**	**V01** **D01** **NA**	**V02** **D03** **NA**	**V03** **D09** **[+2 D]**	**V04** **D29** **[+7 D]**	**V05** **D181** **[+14 D]**
	For all participants				**Only for participants who did not receive a licensed seasonal influenza vaccine during study conduct**
Clinical safety laboratory assessments (20 mL)					
Clinical chemistry (AST, ALT, total and direct bilirubin, C-reactive protein, and creatinine); Hematology (WBC count with differential, hemoglobin, platelet count, and RBC count) **(15 mL)**	SL0001	SL0002	SL0003		
Troponin I **(5 mL)**	SL0001	SL0002	SL0003§		
Clinical immunogenicity assessments (15 mL)					
antibody responses (HAI, NT) (15 mL)	BL0001			BL0004	BL0005
Potential retesting and future research **(5 mL)**	BL0001	BL0002	BL0003	BL0004	
TOTAL	40 mL	25 mL	25 mL	20 mL	15 mL

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, blood sample; D, day, HAI, hemagglutinin inhibition; NT, neutralization test; RBC, red blood cell; SL, safety blood sample; V, visit; WBC, white blood cell.
§Troponin I will not be tested systematically at D09. Troponin I could be tested at D09 in case of abnormal values in previous samples.

Guidance and information for the sample collection, preparation, storage, and shipment will be provided to the study personnel.

8.2 EFFICACY AND IMMUNOGENICITY ASSESSMENTS

Planned timepoints for all immunogenicity assessments are provided in the SoA.

8.2.1 Efficacy Assessments

No clinical efficacy data will be obtained in the study.

8.2.2 Immunogenicity Assessments

Assays will be performed by the Sponsor's laboratory (Swiftwater, PA, USA) or an external testing laboratory under the Sponsor's laboratory responsibility.

8.2.2.1 Hemagglutinin Inhibition (HAI)

Test serum samples and quality control sera (sheep, ferret, and / or human sera) are incubated with Sigma Type III neuraminidase from *Vibrio cholerae* to eliminate non-specific inhibitors. Adsorption of spontaneous anti-species agglutinins are then performed by incubating the test serum samples and quality control sera with a RBC suspension. Following this, the mixtures are centrifuged and the supernatants containing the treated sera are collected for testing. Ten 2-fold dilutions (starting at 1:10) of the treated test serum samples and quality control sera are incubated with a previously titrated influenza antigen at a concentration of 4 hemagglutination units / 25 µL. Influenza antigen is not added to the serum control wells containing only serum and RBCs. The mixture is then incubated and an RBC suspension is added. Following incubation, the results are read. The endpoint of the assay is the highest serum dilution in which complete inhibition of hemagglutination occurred. Each serum sample can either be tested in singleton (ie, one assay run) or in 2 independent assay runs (duplicate) which will include 2 independent samplings of the original serum and 2 independent preparations of influenza virus antigen. The decision to test study samples, either in singleton or duplicate HAI, will be taken by the study team prior to the execution of clinical testing by the laboratory. The lower limit of quantitation (LLOQ) is set at the lowest dilution used in the assay, 1:10. Titers below this level are reported as < 10 (1/dil). If the highest / last serum dilution used in the assay exhibited complete inhibition of hemagglutination, the serum Ab titer is reported as ≥ 10 240 (1/dil).

8.2.2.2 Seroneutralization (SN)

The SN test measures Abs directed against the viral neutralization epitopes of the influenza virus, which may be different from the hemagglutination epitopes; therefore, the SN titers may be different from the HAI titers.

To measure SN, serially diluted, heat-inactivated human serum samples are pre-incubated with a fixed amount of challenge virus prior to the addition of Madin-Darby canine kidney (MDCK) cells. After overnight incubation, the viral nucleoprotein production in infected MDCK cells is measured by enzyme-linked immunosorbent assay (ELISA), using monoclonal Ab specific to either influenza A nucleoprotein or influenza B nucleoprotein. Since serum neutralizing Abs to the influenza virus inhibit the viral infection of MDCK cells, the ELISA optical density results are inversely proportional to the titers of neutralizing Ab present in the serum. The LLOQ is set at the reciprocal of the lowest dilution used in the assay (ie, 10 [1/dil]). Titers below this level are reported as < 10 (1/dil). Titers > 10 240 (1/dil) are pre-diluted, retested, and the end titer is reported.

8.3 SAFETY ASSESSMENTS

This section presents safety assessments other than adverse events which are presented in Section 8.4.

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.3.1 Physical Examinations

At V01, the investigator or a designee will perform a full physical examination. A targeted physical examination, based on medical history may be performed during the other visits. Information will be recorded in the source document.

8.3.2 Vital Signs

Measurement of vital signs will include systolic blood pressure, diastolic blood pressure, and cardiac rhythm (heart rate). Vital signs will be measured at V01 (before and 30 minutes after vaccination) and at each visit to the site. Information will be recorded in the source document.

Oral pre-vaccination body temperature will be measured before vaccination at D01 and will be systematically collected by the investigator on the source document. Tympanic, skin, and temporal artery thermometers must not be used.

8.3.3 Electrocardiograms

An ECG will be performed at V01 to serve as a baseline to identify participants with clinically relevant abnormalities that may affect participant safety or study results. In the event that a participant develops symptoms of myocarditis, pericarditis, and/or myopericarditis during the conduct of the study, additional ECG(s) will be performed as rapidly as possible, at an unscheduled visit, if necessary.

The ECG will be available in the source document. Physician's interpretation of the results will be collected in the CRF.

8.3.4 Clinical Safety Laboratory Tests

- See Appendix 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring after the first study vaccination as an AE. The laboratory results must be retained with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or RMO.
    - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.
    - All protocol-required laboratory tests, as defined in Appendix 10.2, must be conducted in accordance with the SoA (Section 1.3) and the laboratory manual.

- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE), then the results must be recorded.

8.3.5 Pregnancy Testing

Urine or serum pregnancy testing will be performed in women of childbearing potential before vaccination.

See Appendix 10.2 and the SoA (Section 1.3) for the timing and frequency.

8.4 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

The definitions of an AE, SAE, and the different categories of AEs can be found in Appendix 10.3.

AEs will be reported by the participants to the investigator, then by the investigator to the Sponsor.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 10.3.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

Immediate Post-vaccination Observation Period

Participants will be kept under observation for 30 minutes after vaccination to ensure their safety. The post-vaccination observation should be documented in the source document.

Reactogenicity

Solicited injection site reactions will be collected from the day of vaccination (D01) until 7 days after vaccination (D08).

Solicited systemic reactions will be collected from the day of vaccination (D01) until 7 days after vaccination (D08).

The solicited injection site reactions and systemic reactions that are pre-listed in the participant diary and CRF, together with the intensity scales, are presented in Appendix 10.3.5.1.1.

Unsolicited Non-serious Adverse Events

Unsolicited non-serious AEs will be collected from the day of vaccination (D01) until 28 days after vaccination (D29).

The intensity grading scale for unsolicited non-serious adverse events is presented in Appendix 10.3.5.1.2.

MAAEs

MAAEs will be collected from the day of vaccination (D01) until 180 days after vaccination (D181).

AESIs

AESIs will be collected from D01 through the end of the study (ie, D366).

All AESIs will be collected from inclusion until D181 and only related AESIs will be collected from D181 to D366.

See Section 8.4.6 for the list of AESIs.

SAEs

Information on SAEs will be collected and assessed throughout the study, from inclusion (D01) until 365 days after vaccination (D366).

All SAEs will be collected from inclusion until D181 and only fatal SAEs (whatever the relationship) and only related SAEs will be collected from D181 to D366.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 10.3. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

8.4.2 Method of Detecting AEs and SAEs

Individual participant diaries, specifically designed for this study by the Sponsor and provided to the study sites, will be given to study participants for the recording of daily safety information. These participant diaries will include pre-listed terms and intensity scales as well as areas for free text to capture additional safety information or other relevant details. If a paper participant diary was used at the first visit or if there is an issue with the electronic participant diary, paper format (participant diary / memory aid) will be used by the participant for the rest of the study. Participants will also be provided with rulers for measuring the size of injection site reactions, and with standard digital thermometers for measuring daily body temperatures. To ensure consistency of reporting, the study sites will instruct participants on how to correctly use these tools.

At specified intervals, the investigator or a designee will interview the participants to collect the information recorded in the participant diary, and will attempt to clarify anything that is

incomplete or unclear. All clinical study information gathered by the study site will be reported electronically by the investigator or designee using a web-based CRF. Any information that was not documented in the participant diary will first be captured in the source document and then reported electronically.

The 6-month follow-up and the 12-month follow-up should be done at least 180 days and 365 days after the vaccination, respectively, for all participants having received one dose of the study intervention, by interviewing participants either during a visit or over the telephone using a questionnaire to capture all SAEs/AESIs and MAAEs up to D181 and only fatal and related SAEs/AESIs between D181 and D366, if applicable.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts, unless a participant refuses further contact. All AEs that are considered by the investigator as serious, or related to the study intervention administered, or that led to study or vaccination discontinuation, or AESIs (as defined in Section 8.4.6)], will be followed during the conduct of the study until resolution, stabilization, or the participant is lost to follow-up (as defined in Section 7.3). For related SAEs and related AESIs ongoing at last study visit, such follow-up may need to continue after the end of the study.

Further information on follow-up procedures is provided in Appendix 10.3.

8.4.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and/or other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with international/regional and country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

8.4.5 Pregnancy

Pregnant women are not eligible to participate in the study and women of childbearing potential agree to use an effective contraceptive method, as defined in the inclusion criteria. However, a participant could potentially become pregnant during her participation.

- Pregnancies with an estimated conception date up to 12 weeks after study vaccination are to be reported, throughout the study.
- Details of all pregnancies in female participants will be collected after the start of study intervention and until delivery in the GPV database.
- If a pregnancy is reported, the investigator should promptly inform the Sponsor and will record pregnancy information together with the contraceptive method on the appropriate form and submit it to the Sponsor within 1 month of learning of the pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 months beyond the estimated delivery date, but will be in accordance with local regulations. In case of exposed pregnancy, the child will be followed up for safety assessment for 6 months after birth which may be beyond the last visit of the study. If a pregnancy with an estimated conception date behind 12 weeks after study vaccination is reported, the participant will be followed up for safety assessment until the last visit of the study. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

8.4.6 Adverse Events of Special Interest

AESIs will be defined as shown below:

- Anaphylactic reactions (including bronchospasms, and laryngeal spasms)
- GBS, neuritis (including Bell's palsy)
- Myocarditis, pericarditis, and myopericarditis
- Vasculitis

Serious AESIs are a subset of SAEs. Non-serious AESIs are reported to the Sponsor in an expedited manner and collected in the GPV database in the same manner as SAEs, including thorough case documentation (eg. narrative and all complementary safety information).

For each AESI, the standard case definitions from the Brighton Collaboration or US CDC will be used (19) (20) (21) (22).

Acute chest pain, shortness of breath, palpitations, or other signs or symptoms potentially compatible with myocarditis or pericarditis (even if not meeting myocarditis/pericarditis CDC case definition), occurring within 4 to 6 weeks after vaccination should be reported as AESI as soon as myocarditis or pericarditis is not clearly ruled out. Participants reporting signs or symptoms of myocarditis or pericarditis will be referred to a cardiologist or visit to the Emergency department for evaluation and management, as applicable. Cases adjudicated as meeting the definition of myocarditis or pericarditis will be considered as serious and followed until resolution of symptoms and abnormal test findings.

Any AESI reported as related by investigator will be evaluated by SMT without delay. Cases suggestive of myo-/pericarditis will be sent to CAC.

8.4.7 Medically Attended Adverse Events

MAAEs will be collected using the same process as other AEs. See Appendix 10.3.1 for definition of MAAEs.

8.4.8 Medication Errors, Misuses or Abuses of Medicinal Product

Definitions of medication error, misuse or abuse can be found in Appendix 10.5.

Since the study intervention*s* are administered by a health care professional, misuse and abuse are not applicable in this study. Medication errors will be recorded in the GPV database.

8.4.9 Early Safety Data Review

The safety of the study intervention will be continuously monitored by the Sponsor. The enrollment of participants will be performed in a stepwise manner through sentinel cohorts, based on ESDR performed by an internal Sponsor SMT. An internal SMT will review safety data at each step with regards to dose level and age group. In the event of a reactogenicity or safety concern with a particular dose, that dose and higher doses will not be assessed in the affected age group(s) in the main cohort. The enrollment strategy is summarized in Figure 2.

[redacted] The collective D01-D09 data for sentinel cohort 2 and cumulative

safety data from safety cohort 1, will also be analyzed at this time. A GO decision for the enrollment of participants (18-64 years of age and ≥ 65 years of age) in the main cohort will be based on acceptable safety data after ESDR analysis by the SMT. The SMT can also consider data external to the study to decide on progression between sentinel cohort stages and between the sentinel cohort and the main cohort (for example, based on data generated with similar products in other studies).

Of note, in case of enrollment issues, the enrollment of participants aged 18-64 years and 65 years and older may be done independently of each other in both sentinel and main cohorts; in that case, different ESDRs will be done to evaluate D09 data from either participants aged 18-64 years or 65 years and older.

The following safety parameters will be assessed as part of the ESDR:

- Immediate unsolicited non-serious AEs
- Solicited injection site and systemic reactions
- Laboratory abnormalities
- Unsolicited AEs reported as related by the investigator
- MAAEs
- SAEs and AESIs

If any of the following criteria are met in 1 dose group, a decision based on the expedited SMT meeting recommendation will be made as to whether or not enrollment in the group or the study will be allowed to resume:

- ≥ 2 participants develop solicited injection site reactions of ≥ Grade 3, or
- ≥ 2 participants develop solicited systemic reactions considered at least possibly related, and of ≥ Grade 3, or
- ≥ 2 participants have the same laboratory test with an abnormality of ≥ Grade 3 that cannot be explained by underlying disease, or
- ≥ 2 participants develop the same or similar Grade 3 or higher adverse event assessed as being of either possible, probably, or certain causality
- Or other safety concerns in mRNA groups at any dose level (eg., SAE considered related with the vaccine)

Upon completion of evaluation of the sentinel safety cohort as described above, full enrollment of the main cohort may proceed; however, if, at any time, there is a safety concern, the full enrollment for the affected group at that dose level and higher doses will be stopped.

8.4.10 Safety Management Team Review

Safety monitoring by SMT during the main cohort stage will include ongoing monitoring of SAEs and AESIs, as well as periodic aggregate analysis of all safety data at relevant study milestones. The SMT aggregate reviews will be planned at least quarterly during the study active phase, with periodicity driven by recruitment milestones. The blinded Sponsor review is based on preliminary

data entered into eCRF that have not been subject to validation and database lock. The usual and ongoing process of monitoring safety signals outside of those specified in the protocol-defined ESDR will continue unchanged. The SMT is empowered to recommend a pause in both recruitment and / or further vaccination while it investigates any potential signal or concern.

8.4.11 Alert Thresholds

At any time during the recruitment period, if the following events are observed it requires expedited data review and assessment by SMT:

- One participant develops vaccine-related SAE, assessed as being related in the opinion of the investigator and the Sponsor
- One participant develops myocarditis, pericarditis, and / or myopericarditis (as adjudicated by an external CAC), assessed as related to the study vaccine by the investigator and the Sponsor
- One participant develops laryngospasm, bronchospasm, or anaphylaxis within 24 hours after administration of study intervention
- Any AE which, in the opinion of the investigator and the Sponsor, indicates that human participants would be exposed to an unreasonable and significant risk of illness or injury

In addition, for the main cohort, the enrollment will be paused if the following events are observed:

- ≥ 10% (at least 2 participants during enrolment) per treatment group participants develop solicited injection site reactions of ≥ Grade 3, or
- ≥ 10% (at least 2 participants during enrolment) per treatment group participants develop solicited systemic reactions of ≥ Grade 3, or
- ≥ 10% (at least 2 participants during enrolment) per treatment group have the same laboratory test with an abnormality of ≥ Grade 3 that cannot be explained by underlying disease, or
- ≥ 2 participants develop the same or similar Grade 3 or higher adverse event per treatment group assessed as being of either possible, probably, or certain causality

If any of the above criteria is met, a decision based on benefit/risk impact for the participants will be made by the Sponsor as to whether enrollment in the study will be allowed to resume.

8.5 PHARMACOKINETICS

Pharmacokinetics parameters are not evaluated in this study.

8.6 PHARMACODYNAMICS

Pharmacodynamics parameters are not evaluated in this study.

8.7 GENETICS

Genetics are not evaluated in this study.

8.8 BIOMARKERS

No other biomarkers than those described in the immunogenicity assessments section Immunogenicity Assessments

See Section 8.2.2.

8.9 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.10 LEFTOVER BIOLOGICAL SAMPLES

Any unused part of the biological samples collected for this study are being retained in long-term storage (for up to 25 years after the end of the study) to support answers to regulatory questions related to the product's licensure and the potential revalidation of the study results. The biological samples will be securely stored at the Sponsor's laboratory. Relating data will be stored for up to 25 years.

The other biological samples collected to qualify the participants for inclusion in the study or to monitor their health during the study are dedicated for immediate use. If any of these biological samples are not completely used up, they will be destroyed at the latest at the end of the study or after the time requested by local law.

8.11 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease and the development of new vaccines/medicines. Reuse of coded data and biological samples (leftover and additional) will be limited to future scientific research conducted under a research plan for the purpose of diagnosing, preventing or treating diseases. The future research projects will be conducted under the Sponsor's and/or its affiliates' and/or, if applicable, the partner of the Sponsor which has licensed the study intervention to the Sponsor or which is co-developing the study intervention with the Sponsor's control, acting alone or in collaboration with research partners such as universities, research institutions or industrial partners with whom the coded data may be shared.

Data and biological samples will be stored and used for future research only when consented to by participants (see Section 10.1.3) and, when applicable, further information on the future research has been provided to the study participant, unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of samples will not be included in the local ICF). The conditions for reuse will be adapted locally with the appropriate language in the ICF.

In any case, a specific consent will be collected for the performance of genetic analyses on leftover and additional samples.

Data protection – Processing of coded clinical data

The study participants will be provided with all mandatory details of the data processing in the ICF. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

Study participant data for future research will be stored for up to 25 years after the end of the study.

Use of leftover samples and additional samples for future research

Remaining leftover samples will be used only after the study ends, ie end of study as defined in the study protocol. Additional/extra samples must be collected as defined in the SoA and can be used during the study conduct or after the study ends.

The study participants will be provided with all mandatory details of the use of the human biological samples (leftover and additional) in the ICF.

Relating data and biological samples for future research will be stored for up to 25 years after the end of the study.

Any samples remaining at the end of the retention period will be destroyed. If participants request destruction of their samples before the end of the retention period, the investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.

9 STATISTICAL CONSIDERATIONS

The statistical analysis plan (SAP) will be finalized prior to database lock and it will include (if applicable) a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 STATISTICAL HYPOTHESES

No hypotheses will be tested. The analyses will be descriptive.

9.1.1 Multiplicity Adjustment

Not applicable

9.2 ANALYSIS SETS

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Modified Full analysis Set (mFAS)	Participants who have received the study vaccine. Participants will be analyzed according to the intervention they received
Ab Persistence Set	Participants included in the mFAS and who did not receive a licensed seasonal influenza vaccine before visit V05 (D181)

9.3 STATISTICAL ANALYSES

9.3.1 General Considerations

All analyses will be descriptive. Details will be provided in the SAP, if necessary.

9.3.2 Primary Endpoints Analysis

Safety

The safety parameters, including frequencies of immediate reactions, solicited reactions, unsolicited AEs, MAAEs, SAEs, and AESIs will be described by study group with the 95% confidence interval (CIs) for main endpoints of point estimates calculated using the exact binomial distribution (Clopper-Pearson method) for proportions.

In addition, biological safety will be analyzed, counting the presence of out-of-range biological test results (including shift from baseline values for some parameters) and also according to severity grades.

The mFAS will be used for the safety analyses.

Immunogenicity

Immunogenicity endpoints will be summarized by study group with 95% CIs for main endpoints. The 95% CIs for the geometric mean titers (GMTs) and GMT ratios (GMTRs) will be calculated using a normal approximation of log-transformed titers. The 95% CIs for the proportions will be based on the Clopper-Pearson method.

The ratios of GMTs (Group X / Group Y[a]) will be obtained between groups with the 95% CIs calculated using a normal approximation of log-transformed titers. In addition, the ratios of GMTs (Group X / Group Y) will be obtained between groups with the 95% CIs after adjustment on baseline, through linear model for log post-vaccination HAI titers, including group as an independent factor and log pre-vaccination HAI titers as a covariate.

The differences in frequencies between groups (Group X - Group Y) will be computed along with the 2-sided 95% CIs by the Wilson-Score method without continuity correction. Additional parameters may be displayed as appropriate.

Reverse cumulative distribution curves (RCDCs) against each strain will be performed for baseline (D01) and at D29.

The mFAS will be used for the primary immunogenicity analyses.

9.3.3 Secondary Endpoints Analysis

Immunogenicity

Immunogenicity endpoints will be summarized by study group with 95% CIs for main endpoints. The 95% CIs for the GMTs and GMTRs will be calculated using a normal approximation of log-transformed titers. The 95% CIs for the proportions will be based on the Clopper-Pearson method.

The mFAS will be used for the secondary immunogenicity analyses.

9.3.4 Exploratory Endpoints Analysis

[redacted]

9.4 INTERIM ANALYSES

The following sequence analysis will be done:

- Beside the regular safety reviews performed by the Sponsor's unblinded internal safety review committee (see SMT/ESDR section), interim analyses may be conducted in all or a

[a] In term of groups, each QIV mRNA will be compared to each other and to QIV-SD or RIV4 or QIV-HD (as applicable) in all participants and in each age group

subset of participants who completed V04 (D29) for business decisions. These analyses may contain all safety data up to D29 and partial HAI D01 and D29 data.

- An interim analysis may be conducted once the 6-month data (with or without immunogenicity data) have been collected.
- A final analysis will be conducted once all data have been collected, including 12 months safety data, and the final database lock has occurred.

No statistical adjustment will be applied as this is a learning study.

9.5 SAMPLE SIZE DETERMINATION

[redacted]

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Note: The term "participant" is used throughout this protocol and in the DC. However, the term "subject" will be used in the CRF in order to comply with the Clinical Data Interchange Standards Consortium (CDISC) requirements. Similarly, "legally acceptable representative" is used in the protocol whereas "guardian" is used in the CRF.

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- The General Data Protection Regulation (GDPR) and any other applicable data protection laws
- Any other laws and regulations as applicable, eg:
    - The Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014 on clinical trials on medicinal products for human use
    - 21 CFR
- The protocol, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator or the Sponsor (according to local regulations) and reviewed and approved by the IRB/IEC before the study is initiated
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following, as applicable:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC (in addition to summaries required from the Sponsor)
- Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered

unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:

- The return of such information to the study participants (and/or their designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
- The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
- The participant in a clinical study has the right to opt out of being notified by the investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, investigators should seek independent ethical advice before determining next steps.
- In case the participant has decided to opt out, the investigator must record in the site medical files that she/he does not want to know about such findings.

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and if applicable, 21 CFR, Regulation No 536/2014 of the European Parliament and the Council of the European Union for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations

According to the Regulation No 536/2014 of the European Parliament and the Council of the European Union and as specified by the applicable regulatory requirements in non-EU/EAA countries, Sanofi, as the clinical trial Sponsor, needs to report to the concerned regulatory agency/ies serious breaches without undue delay but not later than 7 calendar days of becoming aware of that breach. A serious breach is defined as a deviation of the version of the protocol applicable at the time of the breach or the applicable clinical trial regulation that is likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.

The Sponsor shall ensure that all parties involved in the conduct of the clinical study promptly report any events that might meet the definition of a serious breach.

Therefore, investigators shall, within 48 hours after being aware of a deviation that might meet the definition of a serious breach, report to the Sponsor any suspected serious breach to enable the Sponsor to carry out the required assessment and notify the regulatory agency/ies in the event of a confirmed serious breach. To that extent, the principal investigator must have a process in place to ensure that the site staff or service providers engaged by the principal investigator/institution are able to identify the occurrence of a (suspected) serious breach and that a (suspected) serious breach is promptly reported to the Sponsor through the contacts (e-mail address or telephone number) provided by the Sponsor.

10.1.2 Financial Disclosure

Information related to financial disclosure is described in the investigator's contract.

10.1.3 Informed Consent Process

- The ICF will be provided to the study participant in paper version.
- The investigator or the investigator's representative will explain the nature of the study, including the potential risks and benefits, to the participants and answer all questions regarding the study, including what happens to the participants when their participation ends (post-trial access strategy for the study).
- Potential participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements including those of the GDPR and of the French law, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- The actual ICF used at each center may differ, depending on local regulations and IEC / IRB requirements. However, all versions must contain the standard information found in the sample ICF provided by the Sponsor. Any change to the content of the ICF must be approved by the Sponsor and the IEC / IRB prior to the form being used.
- If new information becomes available that may be relevant to the participants's willingness to continue participation in the study, this will be communicated to them in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study. Where participants are not in the study anymore, the Sponsor must define if those participants must or not re-consent or be informed of the revision (eg, if the processing of personal data is modified, if the Sponsor changes).
- A copy of the ICF(s) must be provided to the participant.

The core ICF contains 2 separate sections that addresses the use for research of participants' data and/or samples (remaining mandatory ones or new extra samples collected for optional research). Optional exploratory research must be detailed in the section "Optional tests/procedures" and future research is to be defined in the core ICF Part 2. Each option is subject to an independent consent and must be confirmed by ticking checkboxes in the core ICF Part 3, each checkbox corresponding to a specific use: consent for the performance of an optional exploratory research; consent for storage and use of coded data for future research; consent for use of leftover samples and associated coded data for future research; consent for collection of additional biological samples for storage and use for future research, and consent for performance of genetic analyses on biological samples. The investigator or authorized designee will explain to each participant the objectives of the exploratory research and why data and samples are important for future research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 10.6: Contingency Measures for a regional or national emergency that is declared by a governmental agency.

10.1.4 Data Protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR. The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant personal data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Participants' race and ethnicity will be collected in this study because these data are required by regulatory agencies (eg, FDA).

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers, when applicable, will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participants as described in the informed consent.
- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between Sponsor, investigators, and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties. Accordingly, the investigator and the institution will promptly notify the Sponsor about any data security breaches and detail in the notification the nature of the breach, the categories (eg, Sponsor's personnel, study participants or their relatives, healthcare professionals, etc.), the approximate number of participants concerned, the type and approximate number of data records concerned and the likely consequences of the breach. The institution and/or investigator will investigate the causes of the data security breach and take actions to minimize the effects of said breach. The institution and/or investigator will record all information relating to the breach, including the

results of their own investigations and investigations by authorities, as applicable, and will take all measures as necessary to prevent future data security breaches.

- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- Participants must be informed that their study-related data will be used for the whole "product development program", ie, for this study as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of personal data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
    - Personnel within Sanofi or partners or service providers involved in the study
    - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
    - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
    - Sanofi's Binding Corporate Rules for intra-group transfers.

- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the Transcelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the Transcelerate project. This sharing allows investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the Transcelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 46 Avenue de la Grande Armée - 75017 PARIS - France (to contact Sanofi by e-mail, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committees Structure

- **Sponsor Safety Management Team (SMT)**

Participant safety will be continuously monitored by the Sponsor's internal safety review committee which includes safety signal detection at any time during the study. The Sponsor's internal safety review committee, led by the GPV representative and the RMO, will be responsible for the unblinded review, assessment, and evaluation of safety data generated from this study. This committee, composed of designated GPV, Clinical, and Biostatistics representatives, is empowered to recommend a pause in recruitment and/or further vaccination while it investigates any potential signal or concern.

- **External Cardiac Adjudication Committee (CAC)**

In the event that a participant develops symptoms of myocarditis, pericarditis, and / or myopericarditis, cardiac monitoring data may be assessed by an external CAC, using standard case definitions to ensure standardized adjudication of cases.

10.1.6 Dissemination of Clinical Study Data and Results

Study participants

At the end of the clinical study, the Sponsor may publish the study results in scientific journal(s). As part of the review for publication, independent scientists may need to use "coded" data of all the study participants to independently verify the study's results.

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other

clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include ClinicalTrials.gov, euclinicaltrials.eu, and sanofi.com, as well as some national registries. For pediatric and adult trials, the results will generally be submitted/released 6 and 12 months respectively, after the end of the clinical trial worldwide (ie, the last active, participating country).

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance, and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to vivli.org.

Individual anonymized participant data and supporting clinical documents are available for request at vivli.org. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: vivli.org.

Professionals involved in the study or in the product development program

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organizations".

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on CRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF Completion Instructions.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be predefined to identify systematic issues that can impact the safety of participants and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

- The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a different retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.
- The protocol will be signed by the RMO, and a Protocol Investigator Agreement Form (PIAF) will be signed by all investigators. The clinical study report will be signed by the RMO and the coordinating investigator. In case no coordinating investigator has been designated, it will be the responsibility of the RMO or designee(s) to identify the signatory investigator.

10.1.8 Source Documents

"Source data" are the data contained in source documents. Source documents are original documents or certified copies, and include, but are not limited to, diary cards, medical and hospital records, screening logs, informed consent / assent forms, telephone contact logs, and worksheets.

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and Site Start and Closure

Study personnel will be informed of which clinical supplies will be provided by the Sponsor or the site.

The study start date is considered the date of the first visit planned in the SoA of the first participant.

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies

have been either destroyed or returned to the Sponsor, all samples are shipped to the appropriate laboratories, the center study-site has all the documents necessary for archiving and a study-site closure visit has been performed along with a Site Close Out Form submitted to the IRB, as required.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development
- Information on the study intervention leads to doubt as to the benefit/risk ratio

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication Policy

Information related to publication policy is described in the investigator's contract.

10.2 APPENDIX: CLINICAL LABORATORY TESTS

- The tests detailed in Table 13 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 13: Protocol-required safety laboratory tests

Laboratory Assessments	Time period for assessment	Parameters
Clinical Chemistry	V01 (D01) before vaccination V02 (D03) V03 (D09)†	Creatinine C-reactive protein (CRP) Aspartate aminotransferase (AST) Alanine Aminotransferase (ALT) Total bilirubin Direct bilirubin Troponin I
Hematology	V01 (D01) before vaccination V02 (D03) V03 (D09)	White blood cell (WBC) count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils Hemoglobin Platelet count Red blood cell (RBC) count
Pregnancy testing	V01 (D01) before vaccination	Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)*

Note: In case of abnormal safety laboratory results, unscheduled visits or additional laboratory assessments or procedures may occur based on Investigator's judgment to ensure the participant's safety

*To be considered of non-childbearing potential, a female must be postmenopausal for at least 1 year or surgically sterile

† Troponin I will not be tested systematically at D09. Troponin I could be tested at D09 in case of abnormal values in previous samples

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease, or more severe than expected for the participant's condition) eg, leading to IMP discontinuation or modification of dosing, and/or fulfilling a seriousness criterion
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- Signs, symptoms, or the clinical sequelae of any medication errors with the IMP

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Other Definitions

Adverse Reaction:

An adverse reaction (AR) is any noxious and unintended response to a study intervention related to any dose.

Immediate Event/Reaction:

Immediate events are recorded to capture medically relevant unsolicited systemic AEs which occur within the first 30 minutes after vaccination.

Reactogenicity / Solicited Reactions:

The **reactogenicity** of a vaccine refers to the property of such vaccine to be able to produce common "expected" adverse reactions (either systemic or at the injection site) and its associated signs and symptoms.

A solicited reaction is an “expected” adverse reaction (sign or symptom) observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRF (eg, injection site pain or headache occurring between the day of vaccination and the next 7 days).

By definition, solicited reactions are considered as being related to the corresponding IMP administered.

For injectable vaccines, solicited reactions can either be solicited injection/administration site reactions or solicited systemic reactions

Injection / Administration Site Reactions:

An injection/administration site reaction is an AR at and around the injection/administration site of the IMP. Injection/administration site reactions are commonly inflammatory reactions.

Solicited injection / administration site reactions are reactions at and around the injection / administration site of the IMP observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRF. It is considered by default as being related to the IMP administered at that site.

Note: « Administration site reaction » term is only to be used for vaccines that are not intended to be administered by injection.

Systemic AR:

Systemic ARs are all ARs that are not injection or administration site reactions. They therefore include systemic manifestations such as headache, fever, as well as localized or topical manifestations that are not associated with the injection or administration site (eg, erythema that is localized but that is not occurring at the injection site).

Solicited systemic reactions are systemic AEs observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRF. Solicited systemic reactions occurring

during the specified collection period are always considered related to the IMP even if there is evidence of alternative etiology.

Unsolicited AE/AR:

An unsolicited AE is an observed AE that does not fulfill the conditions of solicited reactions, ie, pre-listed in the CRF in terms of diagnosis and onset window post-vaccination. For example, varicella or a solicited term such as headache starting after the solicited observation period (eg, headache starting on Day 10 post-vaccination in the case where headache occurring between the day of vaccination and the next 7 days is pre-listed in the protocol and CRF as a solicited reaction).

An unsolicited AR is an unsolicited AE that is considered related to an IMP.

Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

All unsolicited AEs occurring at and around the IMP injection/administration site are to be considered by default as related to the IMP administered at that site and are therefore referred as unsolicited injection/administration site ARs.

All unsolicited AEs which are not at and around the IMP injection/administration site, are referred as systemic unsolicited AE. For each unsolicited systemic AE, the investigator assesses the relationship to the IMP. Systemic AEs assessed as related to IMP are referred as systemic ARs.

Adverse Event of Special Interest (AESI):

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's study intervention or program, for which ongoing monitoring and rapid communication by the investigator to the Sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the study Sponsor to other parties (eg, regulators) might also be warranted.

Medically Attended AE (MAAE):

An MAAE is a new onset or a worsening of a condition that prompts the participant or participant's parent/legally acceptable representative to seek unplanned medical advice at a physician's office or Emergency Department. Physician contact made over the phone or by e-mail will be considered a physician office visit for the purpose of MAAE collection. This includes medical advice seeking during the study visit or routine medical care. This definition excludes pediatric check-ups, follow-up visits of chronic conditions with an onset prior to entry in the study, and solicited reactions.

10.3.2 Definition of SAE

The following SAE definition is in compliance with the full definition of an SAE and includes all the key criteria as defined in ICH E2A and ICHD E2D. Some criteria may not apply to all study populations.

An SAE is defined as any adverse event that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is other medically important event • The term "Other medically important events" refers to events which do not meet any of the above seriousness criteria, but which are considered as serious based on investigator medical judgment • Medical or scientific judgment should be exercised by the investigator in deciding whether expedited reporting is appropriate in other situations such as significant medical events that

may jeopardize the health of the participant or may require intervention to prevent one of the other outcomes listed in the above definition. These important medical events should also usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse, new onset diabetes or autoimmune disease, or suspected transmission of any infectious agent via an authorized medicinal product.

Note: *Serious* and *severe* are not synonymous. The term *severe* is often used to describe the intensity of a specific event as corresponding to Grade 3. This is not the same as *serious,* which is based on participant / event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the CRF pages.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Causal Relationship

By convention, all AEs reported at the IMP injection site (either solicited or unsolicited) and all solicited systemic AEs are considered to be related to the IMP (see definition in Section 6) and therefore are referred to as reactions and do not require the investigator's opinion on relatedness.

- Causal relationship of unsolicited systemic AEs and SAEs will be recorded as follows:

- For non-serious unsolicited systemic AEs (except for non-serious AESIs), relationship to study intervention (IMP) will usually be assessed by the investigator only.
- For SAEs and non-serious AESIs, relationship to study intervention (IMP) will be assessed by both the investigator and the Sponsor (except for injection site reactions at the site of IMP injection which will be related to IMP by default). Sponsor assessment is entered in the GPV database only.
- For SAEs only, the causal relationship to study procedures (related/not related to study procedures) will be assessed by both the investigator and the Sponsor. Sponsor assessment is entered in the GPV database only.

- The investigator is obliged to assess the ***causal relationship*** between each unsolicited systemic AE and the study intervention administered as either ***not related*** or ***related***, based on the following definitions:
- Not related – The AE is clearly / most probably caused by other etiologies such as participants' underlying condition, therapeutic intervention, or concomitant therapy; or the delay between vaccination and the onset of the AE is incompatible with a causal relationship; or the AE started before the vaccination (screening phase, if applicable)
- Related – There is a "reasonable possibility" that the AE was caused by the study intervention administered, meaning that there are facts (evidence) and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

- For causal relationship assessment, the investigator will also consult the IB and/or Product Information, for marketed products.

- The investigator must review and provide an assessment of causal relationship for each unsolicited AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always makes an assessment of causal relationship for every event before the initial transmission of the SAE data to the Sponsor.

- The investigators may change their opinion of causal relationship in light of follow-up information and send an SAE follow-up report with the updated causal relationship assessment.

- The causal relationship assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causal relationship of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, when available the investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally submitted documents. • The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information. • Serious adverse events likely to be related to the study intervention, that persist at the end of the study will be followed up by the investigator until their complete disappearance or the stabilization of the participant's condition. The investigator will inform the Sponsor of the date of final disappearance of the event or the date of "chronicity" establishment.

10.3.4 Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section).

SAE Reporting to the Sponsor via Paper CRF
• The SAE paper CRF can be sent to the Sponsor by one of the following means: • By fax, to the following number: +33 (0) 1 60 49 70 70

- In PDF format to the following e-mail address, using a method of transmission that includes password protection: CL-CPV-Receipt@sanofi.com

- By express mail, to the following address:

  Global Pharmacovigilance, Sanofi Pasteur
  Discovery Drive
  Swiftwater, PA 18370

Using a Verbal Autopsy Questionnaire to Aid in Determining the Cause of Death

- In case of the absence or inadequacy of health information that would allow a thorough evaluation of the causes of the death of a study participant, the verbal autopsy procedure may be triggered by either the investigator or the Sponsor. Detailed instructions on the use of the verbal autopsy questionnaire, as well as the questionnaire itself, will be provided separately.

Safety Emergency Call

If, as per the investigator's judgment, a participant experiences a medical emergency, the investigator may contact the Sponsor's RMO for advice on how to address any study-related medical question or problem. If the RMO is not available, then the investigator may contact the Call Center—available 24 hours a day, 7 days a week—that will forward all safety emergency calls to the appropriate primary or back-up Sponsor contact, as needed. The toll-free contact information for the Call Center will be provided separately.

This process does not replace the need to report an SAE. The investigator is still required to follow the protocol-defined process for reporting SAEs to the GPV Department.

In case of emergency code-breaking, the investigator is required to follow the code-breaking procedures described in Section 6.4.

10.3.5 Assessment of Intensity

The investigator will make an assessment of intensity for each AE reported during the study. An intensity grade will be assigned to each AE. The intensity grading scales used in this study are adapted from the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007".

10.3.5.1 Tables for Clinical Abnormalities

10.3.5.1.1 Solicited AR Intensity Grading Scale

Table 14:Solicited injection site reactions: terminology, definitions, and intensity scales

CRF term (MedDRA lowest level term [LLT])	Injection site pain	Injection site erythema	Injection site swelling
Participant diary term	Pain	Redness	Swelling
Definition	Pain either present spontaneously or when the injection site is touched or injected limb is mobilized	Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling
CRF and participant diary intensity scale*	**Grade 1:** No interference with activity **Grade 2:** Repeated use of an over-the-counter (OTC) pain reliever for more than 24 hours or interferes with activity **Grade 3:** Any use of pain reliever that is not OTC and is only obtained by prescription (eg, narcotic) or prevents daily activity.	**Grade 1:** ≥ 25 to ≤ 50 mm **Grade 2:** ≥ 51 to ≤ 100 mm **Grade 3:** > 100 mm	**Grade 1:** ≥ 25 to ≤ 50 mm **Grade 2:** ≥ 51 to ≤ 100 mm **Grade 3:** > 100 mm

* For pain, the scale will be provided in the participant diary and the intensity will be transcribed in the CRF. For other injection site reactions (erythema and swelling), the classification as Grades 1, 2, or 3 will be applied at the time of statistical analysis; the scale is provided for information purposes only. The actual size of the reaction will be reported in the CRF.

Table 15: Solicited systemic reactions: terminology, definitions, and intensity scales

CRF term (MedDRA lowest level term [LLT])	Fever	Headache	Fatigue	Myalgia	Arthralgia	Chills
Participant diary term	Body temperature	Headache	Tiredness	Muscle aches and pains	Joint pain	Chills
Definition	Elevation of body temperature to ≥°38.0°C (≥ 100.4°F)	Pain or discomfort in the head or scalp. Does not include migraine.	Fatigue is a new symptom of lack of energy, or tiredness. For participants ≥ 5 years of age, this symptom is the primary complaint, is not relieved by rest and it may interfere with the participant's function.	Muscle aches and pains are common and can involve more than one muscle at the same time. Muscle pain can also involve the soft tissues that surround muscles. These structures, which are often referred to as connective tissues, include ligaments, tendons, and fascia (thick bands of tendons). Does not apply to muscle pain at the injection site which should be reported as injection site pain.	Pain in a joint or joints	Sensation of cold

CRF term (MedDRA lowest level term [LLT])	Fever	Headache	Fatigue	Myalgia	Arthralgia	Chills
CRF and participant diary intensity scale*	**Grade 1:** ≥ 38.0°C to ≤ 38.4°C, **or** ≥ 100.4°F to ≤ 101.1°F	**Grade 1:** No interference with activity	**Grade 1:** No interference with activity	**Grade 1:** No interference with activity	**Grade 1:** No interference with activity	**Grade 1:** No interference with activity
	Grade 2: ≥ 38.5°C to ≤ 38.9°C, **or** ≥ 101.2°F to ≤ 102.0°F	**Grade 2:** Repeated use of an over-the-counter (OTC) pain reliever for more than 24 hours or interferes with activity.	**Grade 2:** Some interference with activity	**Grade 2:** Some interference with activity	**Grade 2:** Some interference with activity	**Grade 2:** Some interference with activity
	Grade 3: ≥ 39.0°C **or** ≥ 102.1°F	**Grade 3:** Any use of pain reliever that is not OTC and is only obtained by prescription (eg, narcotic) or prevents daily activity.	**Grade 3:** Significant; prevents daily activity	**Grade 3:** Significant; prevents daily activity	**Grade 3:** Significant; prevents daily activity	**Grade 3:** Significant; prevents daily activity

* For all reactions (except fever), the scale will be provided in the participant diary and the intensity will be transcribed in the CRF. For fever, the body temperature will be recorded, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis based on the unit used to measure the body temperature and the intensity scale.

Important notes for the accurate assessment of body temperature:

Participants are to measure body temperature once per day, preferably always at the same time, and using the same standard unit of the considered country (Celsius or Fahrenheit) consistently. The preferred unit for this study is Fahrenheit (US and Puerto Rico) and Celsius (Honduras). The optimal time for measurement is the evening, when body temperature is the highest. Body temperature is also to be measured at the time of any apparent fever. The observed daily body temperature and the route of measurement are to be recorded in the participant diary, and the highest body temperature will be recorded by the site in the CRF. The preferred route for this study is oral.

10.3.5.1.2 Serious and Non-serious Unsolicited AE Intensity Grading Scale

For measurable unsolicited AEs that are part of the list of solicited reactions, the corresponding scale for solicited reactions will be used (see Section 10.3.5.1.1).

All other unsolicited AEs, including SAEs, will be classified according to the following intensity scale:

- Grade 1: No interference with activity.
- Grade 2: Some interference with activity and not requiring therapeutic medical intervention
- Grade 3: Prevents daily activity and requires therapeutic medical intervention

10.3.5.2 Tables for Laboratory Abnormalities

The predefined intensity thresholds for laboratories abnormalities are shown in Table 16.

Table 16: Intensity thresholds for laboratories abnormalities

Laboratory Endpoint	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	≥ 2.1 or requires dialysis
Precision around the derivation:	*1.5≤ value <1.8*	*1.8≤ value <2.1*	*value ≥2.1*
LFT (ALT, AST) (Increase by factor)	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	≥ 5.1 x ULN
Precision around the derivation:	*1.1xULN≤ value <2.6xULN*	*2.6xULN≤ value <5.1xULN*	*value ≥5.1xULN*
Bilirubin* – with any increase in LFT (Increase by factor)	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	≥ 1.51 x ULN
Precision around the derivation:	*1.1xULN≤ value <1.26xULN*	*1.26xULN≤ value <1.51xULN*	*value ≥1.51xULN*

Laboratory Endpoint	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Bilirubin* – with normal LFT (Increase by factor)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	≥ 2.1 x ULN
Precision around the derivation:	*1.1xULN≤ value <1.6xULN*	*1.6xULN≤ value <2.1xULN*	*value ≥2.1xULN*
CRP – mg/L	3 - 10	10 – ≤ 100	> 100
Precision around the derivation:	*3 ≤ value <10*	*10 ≤ value ≤ 100*	*value > 100*

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; C-reactive protein, CRP; LFT, liver function test
* Will be analyzed conjointly

10.4 APPENDIX: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1) Premenarchal

2) Premenopausal female with permanent infertility due to 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3) Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of

12 months of amenorrhea, confirmation with more than one FSH measurement is required.

- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2 Contraception Guidance

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion/ligation
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
• **Highly Effective Methods[b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation – oral – injectable
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
• **Effective Methods[c] That Are Not Considered Highly Effective** *Failure rate of ≥ 1% per year when used consistently and correctly.*

• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) Considered effective, but not highly effective - failure rate of ≥1% per year. Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction).

10.5 APPENDIX: MEDICATION ERRORS, MISUSES OR ABUSES OF MEDICINAL PRODUCT

All reports of medication error, misuse or abuse in relation to the IMP with or without an AE must be collected and transmitted to the GPV database following standard processes. The Investigator will assess whether or not the medication error, misuse or abuse event has to be reported together with an AE or SAE.

A medication error is an unintended failure in the drug treatment process (ie, mistake in the process of prescribing, storing, dispensing, preparing, or administering medicinal products in clinical practice) that leads to, or has the potential to lead to harm to the participant.

A misuse refers to situations where the medicinal product is intentionally and inappropriately used, ie, not in accordance with the terms of the marketing authorization or outside what is foreseen in the protocol, by the participant for a therapeutic purpose.

An abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects, ie intentional non-therapeutic use of a medicinal product by a participant for a perceived reward or desired non-therapeutic effect including, but not limited to, “getting high” (euphoria).

This includes situations in which a participant was involved or not (eg, even if the error was recognized and intercepted before the participant received or used the product), and whether it resulted in harm to the participant or not.

10.6 APPENDIX: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, terrorist attack) may prevent access to the clinical trial site.

Contingency procedures are suggested below and in Section 2.3.1, Section 5.5, Section 6.5, Section 8, Section 10.1.3 for an emergency that prevents access to the study site, to ensure the

safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with GCP in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.

During the emergency, if the site will be unable to adequately follow protocol mandated procedures, alternative treatment outside the clinical trial should be proposed, and enrollment/randomization of study intervention may be temporarily delayed/halted (see also Section 5.5).

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

- If on-site visits are not possible, remote visits (eg, with home nurses, home health vendor, etc.) may be planned for the collection of possible safety and/or efficacy data
- If on-site visits are not possible visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely
- Use of local clinic or laboratory locations may be allowed

Contingencies implemented due to emergency will be documented.

10.7 APPENDIX: COLLECTION, STORAGE, AND FUTURE USE OF DATA AND HUMAN BIOLOGICAL SAMPLES

10.7.1 Compliance with Member State Applicable Rules for the Collection, Storage and Future Use of Human Biological Samples (Article 7.1h) of EU Regulation 536/2014

This appendix is provided separately.

10.7.2 Compliance with Member State Applicable Rules for the Collection, Storage and Future Use of (Personal) Data (Article 7.1d) of EU Regulation 536/2014

This appendix is provided separately.

10.8 APPENDIX: RISK-BASED APPROACH

ICH E6-R2 guideline for GCP is introducing the « risk-based approach » concept which permits to focus efforts on what is critical for a study and most specifically on Critical Data and Critical Processes. Critical data and processes are defined for the study with associated risks in the Study Risk Management Plan.

10.9 APPENDIX: PROTOCOL AMENDMENT HISTORY

Not applicable.

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12 SPONSOR SIGNATURE PAGE

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